POCKET NOTEBOOK

POCKET MEDICINE

NINTH EDITION

Marc S. Sabatine

The Massachusetts General Hospital Handbook of Internal Medicine

Wolters Kluwer

POCKET NOTEBOOK

MEDICINE

Ninth Edition

Edited by
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PROFESSOR OF MEDICINE
HARVARD MEDICAL SCHOOL

A Massachusetts General Hospital Handbook

Wolters Kluwer

Philadelphia • Baltimore • New York • London
Buenos Aires • Hong Kong • Sydney • Tokyo

Acquisitions Editor: Joe Cho
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Creative Director: Stephen Druding
Prepress Vendor: S4Carlisle Publishing Services

Ninth Edition

9 8 7 6 5 4 3 2 1

Printed in the United States of America

Library of Congress Cataloging-in-Publication Data

ISBN-13: 978-1-975242-94-7

Library of Congress Control Number: 2025911385

shop.lww.com

CONTENTS

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FOREWORD

To the First Edition

It is with the greatest enthusiasm that I introduce *Pocket Medicine.* In an era of information glut, it will logically be asked, “Why another manual for medical house officers?” Yet, despite enormous information readily available in any number of textbooks, or at the push of a key on a computer, it is often that the harried house officer is less helped by the description of differential diagnosis and therapies than one would wish.

Pocket Medicine is the joint venture between house staff and faculty expert in a number of medical specialties. This collaboration is designed to provide a rapid but thoughtful initial approach to medical problems seen by house officers with great frequency. Questions that frequently come from faculty to the house staff on rounds, many hours after the initial interaction between patient and doctor, have been anticipated, and important pathways for arriving at diagnoses and initiating therapies are presented. This approach will facilitate the evidence-based medicine discussion that will follow the workup of the patient. This well-conceived handbook should enhance the ability of every medical house officer to properly evaluate a patient in a timely fashion and to be stimulated to think of the evidence supporting the diagnosis and the likely outcome of therapeutic intervention. *Pocket Medicine* will prove to be a worthy addition to medical education and to the care of our patients.

DENNIS A. AUSIELLO, MD
Physician-in-Chief, Massachusetts General Hospital
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PREFACE

To my parents, Matt and Lee Sabatine; to their namesake grandchildren, Matteo and Natalie; and to my wife, Jennifer

Written by residents, fellows, and attendings, the mandate for *Pocket Medicine* was to provide, in as concise a manner as possible, the key information a clinician needs for the initial approach to and management of the most common inpatient medical problems.

The tremendous response to the previous editions suggests we were able to help fill an important need for clinicians. With this ninth edition come several major improvements. We have updated every topic thoroughly. In particular, we have included recommendations from the latest guidelines for chronic coronary disease and acute coronary syndromes, data on the newest pharmacotherapies for heart failure, and the latest catheter-based approaches for valvular heart disease and atrial fibrillation. We include data on the latest biologic therapy for IBD and new therapies for MASH and chronic kidney disease. We cover the latest molecularly targeted therapies for liquid tumors as well as breast and lung cancer. We continue to expand the discussion of SGLT2i and GLP-1 RA for diabetes and now have a new section on obesity and weight management. As always, we have incorporated key references to the most recent high-tier reviews and important studies published right up to the time *Pocket Medicine* went to press. We welcome any suggestions for further improvement.

Of course, medicine is far too vast a field to ever summarize in a textbook of any size. Long monographs have been devoted to many of the topics discussed herein. *Pocket Medicine* is meant only as a starting point to guide one during the initial phases of diagnosis and management until one has time to consult more definitive resources. Although the recommendations herein are as evidence-based as possible, medicine is both a science and an art. As always, sound clinical judgment must be applied to every scenario.

I am grateful for the support of the house officers, fellows, and attendings at the Massachusetts General Hospital. It is a privilege to work with such a knowledgeable, dedicated, and compassionate group of physicians. I always look back on my time there as chief resident as one of my best experiences. I am grateful to several outstanding clinical mentors, including Hasan Bazari, Larry Friedman, Nesli Basgoz, Eric Isselbacher, and Mike Fifer, as well as the late Roman DeSanctis, Charlie McCabe, Mort Swartz, and Peter Yurchak.

This edition would not have been possible without the help of Kate Brennan, CMPP, my academic coordinator. She shepherded every aspect of the project from start to finish, with an incredible eye to detail to ensure that each page of this book was the very best it could be. This edition also naturally builds on the work of the many contributors to prior editions of *Pocket Medicine*, whom we thank for creating such an impressive foundation.

Lastly, special thanks to my parents for their perpetual encouragement and love and, of course, to my wife, Jennifer Tseng, who, despite being a surgeon, is my closest advisor, my best friend, and the love of my life.

I hope that you find *Pocket Medicine* useful throughout the arduous but incredibly rewarding journey of practicing medicine.

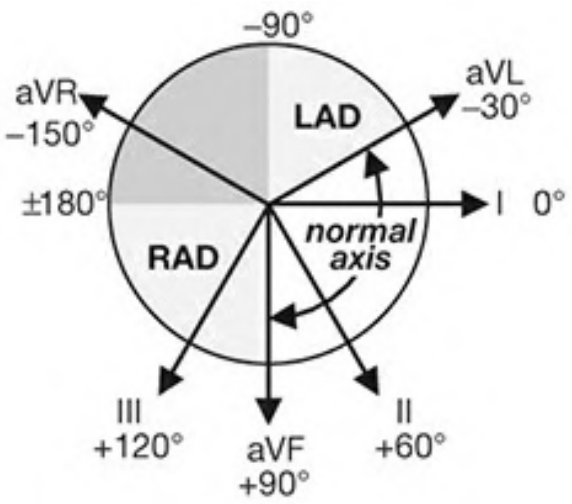
MARC S. SABATINE, MD, MPH

ELECTROCARDIOGRAPHY

Approach (a systematic approach is vital)

- **Rate** (? tachy or brady), **rhythm** (? P waves, regularity, P & QRS relationship)
- **Intervals** (PR, QRS, QT), **axis** (? LAD or RAD), **chamber abnl** (? LAA, RAA, LVH, RVH)
- **QRST changes** (? Q waves, poor R-wave progression V_1–V_6, ST ↑/↓ or T wave Δs)

Figure 1-1 QRS axis

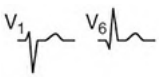
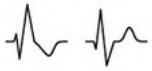


Left axis deviation (LAD)

- **Definition:** axis beyond −30° (S > R in lead II)
- **Etiologies:** LVH, LBBB, inferior MI, WPW
- **Left anterior fascicular block (LAFB):** LAD (–45 to –90°) *and* qR in aVL *and* QRS <120 msec *and* no other cause of LAD (eg, IMI)

Right axis deviation (RAD)

- **Definition:** axis beyond +90° (S > R in lead I)
- **Etiologies:** RVH, PE, COPD (usually not >+110°), septal defects, lateral MI, WPW
- **Left posterior fascicular block (LPFB):** RAD (90–180°) *and* rS in I & aVL *and* qR in III & aVF *and* QRS <120 msec *and* no other cause of RAD

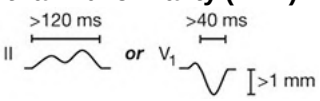
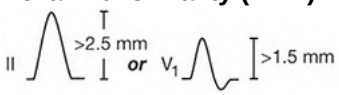
Bundle Branch Blocks (*Circ* 2009;119:e235)		
Normal		Initial depol. left to right across septum (r in V_1 & q in V_6; nb, absent in LBBB) followed by LV & RV free wall, with LV dominating (nb, RV depol. later and visible in RBBB)
RBBB		1. QRS ≥120 msec (110–119 msec = IVCD or “incomplete”)

		2. rSR′ in R precordial leads (V_1, V_2) 3. Wide S wave in I and V_6 4. ± ST↓ or TWI in R precordial leads
LBBB		1. QRS ≥120 msec (110–119 msec = IVCD or "incomplete") 2. Broad, slurred, monophasic R in I, aVL, V_5–V_6 (± RS in V_5–V_6 if cardiomegaly) 3. Absence of Q in I, V_5, and V_6 (may have narrow q in aVL) 4. Displacement of ST & Tw opposite major QRS deflection 5. ± PRWP, LAD, Qw's in inferior leads

Bifascicular block: RBBB + LAFB/LPFB. "Trifascicular block": bifascicular block + 1° AVB.

Prolonged QT interval (*NEJM* 2008;358:169; www.torsades.org)

- Measure QT using threshold method (start of QRS to end of Tw at isoelectric line) or tangent (QRS to where tangent of Tw downslope intersects baseline) when long tail. Use longest QT (often V_2 or V_3) and omit U wave (*Circ* 2018;138:2345).
- QT varies w/ HR → corrected w/ Bazett formula: $QTc = QT/\sqrt{RR}$ (RR = 60/HR, in sec), overcorrects at high HR, undercorrects at low HR (nl QTc <450 msec ♂, <460 msec ♀)
- Fridericia's [$QTc = QT/\sqrt[3]{RR}$] and Framingham [QT_c = QT + 0.154 – (1–RR)] formulae have optimal rate correction
- QT prolongation a/w ↑ risk TdP (espec >500 msec); establish baseline QT and monitor if using QT prolonging meds, no estab guidelines for stopping Rx if QT prolongs
- Etiologies:
  - **Antiarrhythmics:** class Ia (procainamide, disopyramide), class III (amio, sotalol, dofet)
  - **Psych drugs:** antipsychotics (phenothiazines, haloperidol, atypicals), Li, ? SSRI, TCA
  - **Antimicrobials:** macrolides, quinolones, azoles, pentamidine, atazanavir
  - **Other:** antiemetics (droperidol, 5-HT_3 antagonists), alfuzosin, methadone, ranolazine
  - **Electrolyte disturbances:** hypoCa (nb, hyperCa a/w ↓ QT), ± hypoK, ? hypoMg
  - **Autonomic dysfxn:** ICH (deep TWI), Takotsubo, stroke, CEA, neck dissection
  - **Congenital** (long QT syndrome): K, Na, & Ca channelopathies (*Circ* 2013;127:126)
  - **Misc:** CAD, CMP, bradycardia, high-grade AVB, hypothyroidism, hypothermia, BBB

Atrial Abnormalities (*Circ* 2009;119:e251)		
ECG **P-wave criteria**	**Left Atrial Abnormality (LAA)** 	**Right Atrial Abnormality (RAA)** 

Left ventricular hypertrophy (LVH) (*Circ* 2009;119:e251)

- Etiologies: HTN, AS/AI, CMP (HCM, Fabry), coarctation of aorta
- Criteria (all w/ Se <50%, Sp >85%; accuracy affected by age, sex, race, BMI)
  - **Sokolow–Lyon:** S in V_1 + R in V_5 or V_6 ≥35 mm or R in aVL ≥11 mm (↓ Se w/ ↑ BMI)
  - **Cornell:** R in aVL + S in V_3 >28 mm in men or >20 mm in women
  - **Romhilt–Estes point score system** (4 points = probable; 5 points = diagnostic): ↑ volt: limb lead R or S ≥20 mm *or* S in V_1 or V_2 ≥30 mm *or* R in V_5 or V_6 ≥30 mm (3 pts) ST displacement opposite to QRS deflection: w/o dig (3 pts); w/ dig (1 pt) LAA (3 pts); LAD (2 pts); QRS duration ≥90 msec (1 pt) Delayed intrinsicoid deflection (QRS onset to peak of R) in V_5 or V_6 ≥50 msec (1 pt)
  - **If LAD/LAFB:** S in III + max (R+S) in any lead ≥30 mm in men or ≥28 mm in women

Right ventricular hypertrophy (RVH) (*Circ* 2009;119:e251; *JACC* 2014;63:672)

- Etiologies: cor pulmonale, congenital (tetralogy of Fallot, TGA, PS, ASD, VSD), MS, TR
- Criteria [all insensitive, but specific (except in COPD); all w/ poor PPV in general population]
  R > S in V_1 or R in V_1 ≥7 mm, S in V_5 or V_6 ≥7 mm, drop in R/S ratio across precordium
  RAD ≥110° (LVH + RAD *or* prominent S in V_5 or V_6 → consider *biventricular* hypertrophy)

Ddx of dominant R wave in V_1 or V_2

- Ventricular abnl: RVH (RAD, RAA, deep S waves in I, V_5, V_6); HCM; Duchenne's
- Posterior MI: anterior R wave = posterior Q wave; often with inferior or lateral MI
- Abnormal depolarization: RBBB (QRS >120 msec, rSR′); WPW (↓ PR, δ wave, ↑ QRS)
- Other: dextroversion; counterclockwise rotation; lead misplacement; nl variant

Poor R-wave progression (PRWP) (*Am Heart J* 2004;148:80)

- Definition: loss of anterior forces w/o frank Q waves (V_1–V_3); R wave in V_3 ≤3 mm
- Etiologies: old anteroseptal MI (w/ R-wave V_3 ≤1.5 mm, ± persistent ST ↑ or TWI V_2 & V_3)
  LVH (delayed RWP w/ ↑ left precordial voltage); RVH; COPD (may also have RAA, RAD, limb lead QRS amplitude ≤5 mm, $S_I S_{II} S_{III}$ w/ R/S ratio <1 in those leads)
  LAFB/LBBB; WPW; clockwise rotation of the heart; lead misplacement; CMP; PTX

Pathologic Q waves

- Definition: ≥30 msec (≥20 msec V_2–V_3) or >25% height of R wave in that QRS complex
- Small (septal) q waves in I, aVL, V_5 & V_6 are nl, as can be isolated Qw in III, aVR, V_1
- "Pseudoinfarct" pattern may be seen in LBBB, infiltrative dis., HCM, COPD, PTX, WPW

ST elevation (STE) (*NEJM* 2003;349:2128; *Circ* 2009;119:e241 & e262)

- **Acute MI:** upward convexity STE (ie, a "frown") ± TWI (or prior MI w/ persistent STE)
- **Coronary spasm:** Prinzmetal's angina; transient STE in a coronary distribution
- **Pericarditis:** diffuse, upward concavity STE (ie, "smile"); PR ↓; Tw often upright; no Qw
- **HCM, Takotsubo CMP, myocarditis,** LV aneurysm, cardiac contusion
- **Pulmonary embolism:** occ. STE V_1–V_3; classically a/w TWI V_1–V_4, RAD, RBBB, $S_I Q_{III} T_{III}$
- **Repolarization abnormalities:**
  LBBB (↑ QRS duration, STE discordant from QRS complex; see "ACS" for dx MI in LBBB);
  LVH (↑ QRS amplitude); Brugada pattern (rSR′, downsloping STE V_1–V_2); pacing;
  hyperkalemia (↑ QRS duration, tall Ts, no P's); epsilon waves (late afterdepol.) in ACM
- **aVR:** STE >1 mm a/w ↑ mortality in STEMI; STE aVR > V_1 a/w left main disease vs. multivessel disease (LM equivalent)
- **Early repolarization:** most often seen in V_2–V_5 in young adults (*Circ* 2016;133:1520)
  1–4 mm elev of notch peak or start of slurred downstroke of R wave (ie, J point); ± up concavity of ST & large Tw (∴ ratio of STE/T wave <25%; may disappear w/ exercise)
  ? early repol in inf leads may be a/w ↑ risk of VF (*NEJM* 2009;361:2529; *Circ* 2011;124:2208)

ST depression (STD)

- **Myocardial ischemia** (± Tw abnl)
- **Acute true posterior MI:** posterior STE appearing as anterior STD (± ↑ R wave) in V_1–V_3 ✓ posterior ECG leads; manage as a STEMI with rapid reperfusion (see "ACS")
- Repolarization abnl a/w LBBB or LVH (usually in leads V_5, V_6, I, aVL, called "LV strain")
- Digitalis effect (downsloping ST ± Tw abnl, *not* correlated w/ dig levels); hypoK (± U wave)

T-wave inversion (TWI; **≥1** mm; "deep" if **≥**5 mm; normal in III, V_1, aVR) (*Circ* 2009;119:e241)

- Ischemia/MI; *Wellens' sign* (deep, symm precordial TWI) → critical prox LCA lesion; *de Winter's* sign (hyperacute Tw ± upsloping STD V_2–V_6) → acute prox LAD occlusion
- Myopericarditis; CMP (Takotsubo, ARVC, apical HCM); MVP; PE (espec if TWI V_1–V_4)
- Repolarization abnl in a/w LVH/RVH ("strain pattern"); BBB; nl variant if QRS predom. ⊖
- Posttachycardia or postpacing ("memory" T waves)
- Electrolyte, digoxin, P_aO_2, P_aCO_2, pH/core temp Δ's, intracranial bleed ("cerebral Tw")

Low voltage

- QRS amplitude (R + S) <5 mm in all limb leads & <10 mm in all precordial leads
- Etiol: COPD, pericardial/pleural effusion, myxedema, ↑ BMI, infiltrative CMP, diffuse CAD

Electrolyte abnormalities

- ↑ **K:** tented Tw, ↓ QT, ↑ PR, AVB, wide QRS, STE; ↓ **K:** flattened Tw, U waves, ↑ QT
- ↑ **Ca:** ↓ QT, flattened Tw & Pw, J point elevation; ↓ **Ca:** ↑ QT; Tw Δs

ECG in young athletes (*JACC* 2017;69:805)

- Normal patterns may include LVH, RVH, early repolarization
- Evaluate if: arrhythmia, HR <30, ↑ QT, ε/δ waves, LBBB, Brugada pattern, QRS >140 ms, PR >400 ms, Mobitz II, 3° AVB, ST depression, TWI

CHEST PAIN

Disorder	Typical Characteristics & Diagnostic Studies
	Cardiovascular Causes
Angina/ACS (<10% of chest pain in ED)	Substernal "pressure" (⊕ LR 1.3) → neck, jaw, arm (⊕ LR 1.3–1.5) Sharp, pleuritic, positional, or reprod. w/ palp all w/ ⊕ LR ≤0.35 Diaphoresis (⊕ LR 1.4), dyspnea (⊕ LR 1.2), a/w exertion (⊕ LR 1.5–1.8) ≈ prior MI (⊕ LR 2.2); ↓ w/ NTG/rest (but not reliable; *Annals EM* 2005;45:581) ± ECG Δs: STE, STD, TWI, hyperacute Tw, Qw. ± ↑ Troponin.
Pericarditis & myo-pericarditis	Sharp pain → trapezius, ↑ w/ respiration, ↓ w/ sitting forward. ± Pericardial friction rub. ECG Δs (diffuse STE & PR ↓, opposite in aVR) ± pericardial effusion. If myopericarditis, same as above + ↑ Tn and ± s/s HF and ↓ EF.
Aortic dissection	Sudden severe tearing pain (absence ⊖ LR 0.3). ± Asymm (>20 mmHg) BP or pulse (⊕ LR 5.7), focal neuro deficit (⊕ LR >6), AI, widened mediast. on CXR (absence ⊖ LR 0.3); false lumen on imaging.
PE	Sudden pleuritic pain. ↑ RR & HR, ↓ S_aO_2, ECG Δs (sinus tach, RAD, RBBB, $S_IQ_{III}T_{III}$, TWI V_1–V_4, occ STE V_1–V_3), + CTA or V/Q, ± ↑ Tn/BNP.
Pulm HTN	Exertional pressure, DOE. ↓ S_aO_2, loud P_2, RV heave, right S_3 and/or S_4.
	Pulmonary Causes
Pneumonia	Pleuritic; dyspnea, fever, cough, sputum. ↑ RR, crackles. CXR infiltrate.
Pleuritis	Sharp, pleuritic pain. ± Pleuritic friction rub.

PTX	Sudden, sharp pleur pain. Hyperresonance, ↓ breath sounds. Dx w/ CXR.
GI Causes	
Esoph reflux	Substernal burning, acid taste in mouth, ↑ by meals. See "GERD."
Esoph spasm	Intense substernal pain. ↑ w/ swallow, ↓ by NTG/CCB. Dx w/ manometry.
Mallory-Weiss	Esoph tear precipitated by vomiting. ± Hematemesis. Dx w/ EGD.
Boerhaave	Esoph rupture. Severe pain, ↑ w/ swallow. Mediastinal air palpable & on CT.
PUD	Epigastric pain, relieved by antacids. ± GIB. Dx w/ EGD, ± *H. pylori* test.
Biliary dis.	RUQ pain, N/V. ↑ by fatty foods. Dx w/ RUQ U/S, CT, MRCP; ↑ LFTs.
Pancreatitis	Epigastric/back discomfort. Dx w/ ↑ amylase & lipase; abdominal CT.
Musculoskeletal and Miscellaneous Causes	
Costochond	Localized sharp pain. ↑ w/ movement. Reproduced by palpation.
Zoster	Intense unilateral sharp/burning pain. Pain may precede dermatomal rash.
Anxiety	"Tightness," dyspnea, palpitations, other somatic symptoms

(*Braunwald's Heart Disease*, 12th ed, 2022; *JAMA* 2015;314:1955)

Initial diagnostic studies

- **Focused history:** quality, severity, location, radiation; provoking/palliating factors; intensity at onset; duration, freq, & pattern; setting; assoc sx; cardiac hx & risk factors
- **Targeted exam:** VS (incl. BP in both arms); gallops, murmurs, rubs; signs of vascular dis. (carotid/femoral bruits, ↓ pulses) or CHF; lung & abd. exam; chest wall for reproducibility
- **12-lead ECG:** obtain w/in 10 min; comp to priors & obtain serial ECGs; consider *posterior leads* (V_7–V_9) if hx c/w ACS but stnd ECG unrevealing or ST ↓ V_1–V_3 & pain refractory
- **Troponin:** *>99th %ile w/ rise and/or fall in approp. setting is dx of AMI* (*Circ* 2018;138:e618)
  High-sens Tn (hsTn) detectable 1 h after injury, peaks ~24 h, can be elevated for >1 wk
  ✓ at presentation & 1–2 h later; repeat if clinical or ECG Δs; assess absolute level & Δ
  Ddx: *MI* (type 1 [plaque rupture] or 2 [supply–demand mismatch not due to Δ in CAD]), *non-ischemic cardiac* (eg, myocarditis, ADHF, Takotsubo, defibrillation, contusion), *systemic illness* (eg, PE, PHT, stroke, SAH, critical illness)
- **CXR;** other imaging (echo, PE CTA, etc.) as indicated based on H&P and initial testing

Initial approach (*Circ* 2021;144:e368)

- R/o life-threatening causes (ACS, PE, aortic dissection, myopericarditis, etc.)
- If possible ACS, risk-stratify w/ clinician decision pathway (clinical factors + ECG + Tn)
- **Low prob ACS** (eg, H&P unconcerning, ⊖ ECG & Tn): d/c to home; risk factor mgmt
- **Intermed prob ACS** (neither low nor high clinical risk, ± borderline Tn): ✓ TTE and
  If no known CAD → CCTA or stress (former ↓ LOS c/w fxnal testing; *NEJM* 2012;366:1393)
  If recent mildly ⊕ stress or known nonobstructive CAD → CCTA
  If obstructive but not high-risk CAD → stress test
  If recent mod-severely ⊕ stress or high-risk CAD (LM, prox LAD, MVD) → invasive angio
- **High prob ACS** (eg, ECG Δs, ⊕ Tn, new ↓ LVEF): invasive coronary angiography
- Pts w/ acute CP: CCTA vs. stress testing → ↓ time to dx & LOS (less so in era of hsTn), but ↑ probability of cath/PCI (*NEJM* 2012;366:1393 & 367:299; *JACC* 2013;61:880)

NONINVASIVE EVALUATION OF CAD

Stress testing (*J Nucl Cardiol* 2016;23:606; *EHJ* 2020;41:407)

- **Indications:** evaluate possible CAD sx or Δ in clinical status in Pt w/ known CAD, risk-stratify after chest pain, evaluate exercise tolerance, localize ischemia (imaging required)
- **Contraindications** (*Circ* 2002;106:1883 & 2012;126:2465)
  - **Absolute:** AMI w/in 48 h, high-risk UA, acute PE, severe sx AS, uncontrolled HF, uncontrolled arrhythmias, severe HTN (SBP >200), myopericarditis, acute AoD
  - **Relative** (discuss with stress lab): left main CAD, mod symptomatic valvular stenosis, HCM w/ LVOT obstruction, high-degree AVB, severe electrolyte abnl

Exercise tolerance test (w/ ECG alone)

- Generally preferred if Pt can meaningfully exercise; ECG Δs w/ Se ~65%, Sp ~80%
- Typically via treadmill w/ Bruce protocol (modified Bruce or submax if decond. or recent MI)
- Hold anti-isch. meds (eg, nitrates, βB) if dx'ing CAD but give to assess adequacy of meds

Pharmacologic stress test (nb, requires imaging because ECG not interpretable)

- Use if no/low exercise tolerance, recent MI. Se & Sp ≈ exercise. Preferred if LBBB, WPW, or V-paced, because higher prob of false ⊕ imaging with exercise.
- *Coronary vasodilator* (regadenoson [↓ side effects], dipyridamole, adenosine): diffuse arteriolar dilation → relative perfusion defect in vessels w/ fixed epicardial dis. Reveals flow-limiting CAD w/ coronary vasodilation which does not always correlate to ischemia w/ exercise. Side effects: flushing, ↓ HR, AVB, SOB, bronchospasm, ↓ seizure threshold.
- *Chronotropes/inotropes* (dobuta): more physiologic, but longer test; may precip arrhythmia

Imaging for stress test

- Use if uninterp. ECG (V-paced, LBBB, resting ST ↓ >1 mm, digoxin, LVH, WPW), ECG test indeterminate, requires pharm test, or to localize ischemia (eg, prior coronary revasc)
- Radionuclide myocardial perfusion imaging w/ images obtained at rest & w/ stress
  SPECT (eg, ^{99m}Tc-sestamibi): Se ~85%, Sp ~80%
  PET (rubidium-82): Se ~90%, Sp ~85%; requires pharmacologic stress, not exercise
  ECG-gated imaging allows assessment of regional LV fxn (sign of ischemia/infarction)
- **Echo** (exercise or dobuta): Se ~80%, Sp ~85%; no radiation; operator dependent
- **MRI**: Se ~85%, Sp ~90%; requires pharmacologic stress, not exercise

Test results

- **HR** (must achieve ≥85% of max pred HR [220 − age] for *exer.* test to be dx), **BP** response, peak **double product** (HR × BP; nl >20k), HR recovery ($HR_{peak} - HR_{1\ min\ later}$; nl >12)
- **Max exercise capacity** achieved (METS or min); **occurrence of symptoms**
- **ECG Δs:** *downsloping* or *horizontal* ST ↓ (≥1 mm) 60–80 ms after QRS predictive of CAD (but does *not* localize ischemic territory); however, STE highly predictive & localizes
- **Imaging:** radionuclide defects or regional WMA on TTE: reversible defect = ischemia; fixed defect = infarct; transient isch dilation → ? severe 3VD. False ⊖: balanced (3VD) ischemia.
  Coronary flow reserve (PET) →? microvasc dysfxn if ⊖ epicardial CAD (*EHJ* 2020;41:3504).

High-risk test results (PPV ~50% for LM or 3VD, ∴ consider coronary angio)

- ECG: ST ↓ ≥2 mm *or* ≥1 mm in stage 1 *or* in ≥5 leads *or* ≥5 min in recovery; ST ↑; VT

- Physiologic: ↓ or fail to ↑ BP, <4 METS, angina during exercise; ↓ EF
- Radionuclide: ≥1 lg or ≥2 mod. reversible defects, transient LV cavity dilation, ↑ lung uptake

Myocardial viability (*Circ CV Imaging* 2020;13:e53)

- Goal: identify hibernating myocardium that could regain fxn w/ revasc
- Options: **MRI** (Se ~95%, Sp ~50%), **FDG-PET** (Se ~90%, Sp ~65%), **dobutamine stress echo** (Se ~80%, Sp ~80%); **SPECT/rest–redistribution** (Se ~85%, Sp ~65%)
- However, presence of viability has not been shown to predict clinical benefit of revasc.

Coronary CT angiography (*JCCT* 2021;15:192)

- *Gated* CT for contrast enhancement in coronary arteries, NTG given to dilate coronaries. β-blockers commonly used to lower HR.
- CAD–RADS score in stable CP improves risk stratif. of CV events (*JACC Img* 2020;13:1534)
- In stable outPt w/ CP: CCTA added to stnd of care → ↑ early but not overall angio or revasc; ↑ use of preventive med Rx, and ↓ coronary death/MI by 10 y (*Lancet* 2025;405:329). CCTA vs. fxnal testing: no Δ in clinical outcomes overall, but ? ↓ CV death/MI in DM *(NEJM* 2015;372:1291; *JACC* 2019;73:893). In stable CP referred for angio, CCTA vs. invasive with no Δ in CV events (*NEJM* 2022;386:1591).
- CT-FFR: estimates fxnal signif of lesions

Coronary artery calcium (CAC) score

- Quantifies extent of calcium; thus, *estimates* plaque burden (but *not* % coronary stenosis)
- CAC sensitive (91%) but not specific (49%) for presence of CAD; high NPV to r/o CAD
- In intermediate-risk or selected borderline-risk adults (ie, 10-year ASCVD risk of 5–20%), if decision about statin remains uncertain, reasonable to use CAC score to help guide

CORONARY ANGIOGRAPHY & PCI

Precath checklist

- Peripheral arterial exam (radial, fem, DP, PT pulses; bruits); palmar arch eval (eg, w/ pulse oximetry & plethysmography) not routine. ✓ can lie flat × hrs, NPO >6 h, hold metformin and OAC, hold SGLT2i (DKA), preRx w/ steroids + antihist if contrast allergy.
- ✓ CBC, PT-INR (ideally ≤2), Cr; hold ACEI/ARB if renal dysfxn. Blood bank sample.
- ↓ risk of contrast-induced kidney injury: hold ACEI/ARB/ARNI, NSAIDs, diuretics. PreRx w/ isotonic IVF: data mixed but may be helpful if high risk (*Lancet* 2017;389:1312).

Vascular access

- Radial access preferred: ↓ mortality, bleeding, & vascular complications (*Circ* 2022;146:1329)
- Femoral artery commonly used; high puncture ↑ risk of retroperitoneal bleed; low puncture ↑ risk of arterial complic. (eg, AV fistula, superficial femoral artery cannulation)

Periprocedural pharmacotherapy for PCI

- **ASA** 325 mg × 1. **$P2Y_{12}$ inhibitor**: ticagrelor or prasugrel preferred over clopi in ACS. Outside of STEMI, preRx not recommended when anatomy unknown and short time to PCI. Cangrelor (IV $P2Y_{12}$ inhib) ↓ peri-PCI events vs. clopi w/o PreRx (*NEJM* 2013;368:1303).
- GP IIb/IIIa inhibitor: sometimes added if periprocedural thrombotic complication

- **Anticoagulant:** UFH or bivalirudin typically given during case and stopped at end

PCI and peri-PCI interventions

- *Physiology:* fractional flow reserve (FFR): ratio of max flow (induced by adenosine) distal vs. prox to stenosis to ID hemodyn. signif. lesions (≤0.80). Instantaneous wave-free ratio (iFR) similar, doesn't require vasodilator; iFR threshold ≤0.89. Their use ↓ # stents and MACE vs. angio alone (*NEJM* 2009;360:213; 2017;376:1813 & 1824).
- *Advanced imaging:* intravascular U/S (IVUS) or optical coherence tomography (OCT) ↓ MACE (*Lancet* 2024;403:824 & 1855;404:1029)
- Drug-eluting stents (DES): ↓ cardiac death, MI, repeat revasc, & stent thrombosis vs. BMS (*Lancet* 2019;393:2503). Balloon angioplasty alone reserved for lesions too narrow to stent.

Peri-PCI complications

- No or slow reflow, coronary artery spasm: Rx with local delivery of vasodilators
- Coronary artery dissection: treat with stent
- Coronary perforation: immediate balloon tamponade, ✓ for effusion, seal w/ covered stent

Vascular access post-PCI complications

- Postprocedure ✓ vascular access site, distal pulses, ECG, CBC, Cr
- **Bleeding**: reverse/stop anticoag (d/w interventionalist); IV fluids/PRBC/plts as required
  hematoma/overt bleeding: **manual compression**
  retroperitoneal bleed: may p/w ↓ Hct ± flank or back pain. CT abd/pelvis (I^-) or angio if unstable. If does not auto-tamponade, intravascular balloon and/or covered stent.
- **Vascular damage** (~1% of dx angio, ~5% of PCI; *Circ* 2007;115:2666)
  pseudoaneurysm: triad of pain, expansile mass, systolic bruit; diagnose w/ U/S; Rx (if pain or >2 cm): U/S-directed thrombin injection, surgery if former fails
  AV fistula: continuous bruit; Dx: U/S; Rx: surgical repair if large or sx
  limb ischemia (emboli, dissection, clot): cool, mottled extremity, ↓ distal pulses; Dx: loss of pulses, ↓ pulse volume recording, angio; Rx: percutaneous or surgical repair
  radial artery occlusion: if sx, consider 4 weeks LMWH

Other complications (*NEJM* 2017;377:1513)

- **Contrast-induced AKI:** w/in 48 h, peak 3–5 d; pre-hydration reasonable (see "CIAKI")
- **Stroke**: ~0.1–0.4% of cases. Usually ischemic from atheroembolic event during cath. Rx depends on sx/location/timing but includes thrombectomy, tPA, DAPT if ischemic.
- **Cholesterol emboli syndrome**: typically in Pts w/ large burden Ao atheroma; mesenteric ischemia (abd pain, LGIB, pancreatitis); intact distal pulses but livedo and toe necrosis

Stent post-PCI complications

- **Stent thrombosis:** acute clot formation in stent usually in 1st mo but can occur anytime. Typically p/w AMI. Often due to premature d/c antiplt Rx or mech prob. (stent underexpansion or unrecognized dissection, typically presents early).
- **In-stent restenosis:** develops in previously stented segment mos after PCI. Typically p/w gradual ↑ angina. Due to elastic recoil and neointimal hyperplasia; ↓ w/ DES.

Duration of dual antiplatelet therapy (*Circ* 2022;145:e18 & *EHJ* 2018;39:213)

- Determined by presentation (ACS vs. CCD) and ischemic (Pt & procedural) & bleeding risk
- DAPT (ASA 81 + $P2Y_{12}$ inhib) in CCD ideally for ≥3–6 mo. In ACS (qv) default is 1 yr; ASA d/c after 1–3 mos ↓ bleed w/o ↑ MACE. After full course of DAPT, clopi monoRx more efficacious & safer than ASA monoRx (*Lancet* 2025;405:1252).

- If oral anticoag, clopi+DOAC and stop ASA after 1–4 wks to ↓ bleed (*JAMA Cardiol* 2020;5:582). Consider OAC monoRx in low-risk Pts after 12 mos.

CHRONIC CORONARY DISEASE

Definition

- CCD (aka, stable ischemic heart disease) refers to asx and stably sx Pts as well as low-risk new-onset chest pain felt to be due to IHD; excludes rapidly progressive sx or ACS

Noninvasive testing (*Circ* 2021;144:e368 & 2023;148:e20)

- Noninvasive dx testing most valuable when pretest probability is *intermediate* (variably defined as anywhere from 30–70% to 10–90%); typically test if pretest probability >15%
- Several pretest probability scores that take into account age, sex, nature of sx, risk factors
- Exercise ECG testing or CAC reasonable in some low-risk Pts
- In intermediate/high-risk Pts, stress test w/ imaging or CCTA (see "Noninv Eval of CAD")
- If known nonobstructive CAD & stable chest pain: stress testing or CCTA ± FFR
- If obstructive CAD & stable chest pain: stress testing or invasive angio if high-risk CAD

Coronary angiography for CCD (*Circ* 2014;130:1749)

- High-risk noninvasive testing results suggestive of left main or multivessel CAD
- Angina that is refractory to optimal medical therapy
- Uncertain dx after noninvasive testing, occupational need (eg, pilot)
- Unexplained heart failure, ↓ EF, SCD, or life-threatening ventricular arrhythmia

Major risk factor modification (*Circ* 2023;148:e29)

- **LDL-C <70 (or 55) mg/dL**: statin ± EZE, bempedoic acid, PCSK9i (see "Dyslipidemia")
- **BP <130/80** (see "Hypertension"); in CCD may opt for ACEI and βB (if angina)
- **Diabetes** management (qv): GLP1-RA ± SGLT2i; Hb_{A1c} ≤7%
- **Smoking cessation**; influenza vaccine
- **BMI**: 18.5–24.9 kg/m^2; if overweight, GLP-1RA ↓ MACE (*NEJM* 2023;389:2221)
- Diet: ↑ vegetables, fruits, whole grains; ↓ sat. fat, *trans* fatty acids, sweets, red meat, Na; Mediterranean diet ↓ MACE (*Lancet* 2022;399:1876). 150 min/wk mod physical activity.

Optimal medical therapy (OMT) (*Circ* 2023;148:e37)

- **Antiplt Rx:** ASA ~81 mg/d *or* $P2Y_{12}$ inhib (↓ bleeding & ≅ MACE vs. ASA; *JACC* 2023;82:89)
  - DAPT post-PCI & ACS (qv). Prolonged DAPT in CCD w/o MI but w/ DM ↓ MACE but ↑ bleeding (*NEJM* 2019;381:1309).
  - If AF, a/c w/o vs. w/ antiplt ↓ bleeding w/o ↑ MACE (*JACC* 2025;85:1189)
- **βB** if ↓ EF; conflicting data for routine long-term use (*NEJM* 2024;390:1372 & 391:1277)
- **ACEI** (or ARB if intolerant of ACEI) if HTN, DM, CKD, or ↓ EF (*Lancet* 2006;368:581)
- Rivaroxaban 2.5 mg bid + ASA 100 mg/d: 24% ↓ CV events and 18% ↓ death vs. ASA alone, but ↑ major bleeding (*NEJM* 2017;377:1319)
- Colchicine (0.5 mg/d): conflicting data regarding benefit (*NEJM* 2020;383:1838 & 2025;392:633)

Medical therapies for symptomatic relief (*Circ* 2023;148:e59)

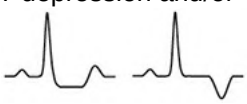
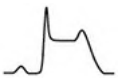
- **Beta-blockers** *1st-line therapy*; CCB (except short-acting dihydropyridines)

- **Long-acting nitrates**
- Ranolazine (↓ late inward Na+ current to ↓ myocardial demand): 2nd-line anti-anginal

Revascularization (*JAMA* 2021;325:1765; *Circ* 2022;145:e18 & 2023;148:e61; *Lancet* 2023;401:1611)

- OMT should be initial focus if stable & w/o evidence of critical anatomy & w/ normal EF
- Goal of revasc should be to ↓ risk of CV morbidity & mortality or to relieve refractory sx
- PCI ↓ anginal sx vs. sham procedure for Pts not on anti-anginal Rx (*NEJM* 2023;389:2319)
- *Older studies:* survival benefit w/ revasc (CABG) vs. med Rx (pre-statin) if: LM disease (≥50% stenosis); 3VD (≥70% stenoses) especially if ↓ EF, 2VD w/ critical proximal LAD
- More recent studies have reevaluated benefit of revasc and PCI vs. CABG
- **MVD & LVEF <35%**: CABG vs. med Rx ↓ mortality by 16%, CV mortality by 21%, and hosp for HF by ~20% after median of 10 yrs (*NEJM* 2016;374:1511). In contrast, PCI did *not* ↓ CV mortality or hosp for HF, but did ↓ spont. MI & unplanned revasc (*NEJM* 2022;387:1351).
- **MVD & DM**: CABG (but not PCI) ↓ risk of MACE by ~25% (*NEJM* 2009;360:2503). In head-to-head comparison, CABG vs. PCI ↓ risk of death or MI, but ↑ stroke (*NEJM* 2021;367:2375).
- **MVD or LM**: CABG vs. PCI ↓ risk of MI & repeat revasc; ? ↓ CV death if complex coronary anatomy, but less clear in current era (*Lancet* 2018;391:939; 2021;398:2247; 2025;405:1481)
- In Pts w/o LM disease & nl LVEF, revasc (largely if not exclusively PCI) vs. OMT did not Δ risk of death, ↑ peri-PCI MI, and ↓ spontaneous MI. Magnitude of benefit tended to be greater in those w/ multivessel disease, prox LAD disease, diabetes, and LVEF 35–45% (*NEJM* 2007;356:1503 & 2020;382:1395; *Circ* 2020;142:1725).
- Recs vary by professional societies (*Circ* 2023;148:e61; *EHJ* 2024;45:3415), but generally:
  - Lifestyle-limiting angina after OMT
  - LM (≥50% stenosis): CABG preferred over PCI unless low SYNTAX score
  - MVD w/ EF <35% or DM: CABG (? PCI if very high surgical risk)
  - 3VD: CABG preferred over PCI if intermediate or high SYNTAX score
  - Proximal LAD stenosis: PCI or CABG
  - Heart Team approach recommended if PCI vs. CABG unclear (esp. complex 3VD)

ACUTE CORONARY SYNDROMES

Spectrum of Acute Coronary Syndromes			
Dx	**UA**	**NSTEMI**	**STEMI**
Coronary thrombosis	Subtotal occlusion		Total occlusion
History	Angina that is new-onset, crescendo, or at rest; usually <30 min		Angina at rest
ECG	± ST depression and/or TWI 		ST elevations 
Troponin/CK-MB	⊖	⊕	⊕ ⊕

Ddx (causes of myocardial ischemia/infarction other than atherosclerotic plaque rupture)

- **Ischemia w/o plaque rupture** ("type 2" MI): ↑ demand (eg, ↑ HR), ↓ supply (eg, HoTN). More likely in older, ♀, non-CAD comorbidities (CKD, etc.) (*JACC* 2021;77:848). Distinguishing from ACS is

clinical dx; angiography is gold standard.

- **Nonatherosclerotic coronary artery disease** (*JACC* 2018;72:2231)
  - Spasm: Prinzmetal's variant, cocaine-induced (6% cocaine users w/ chest pain r/i for MI)
  - Dissection: spontaneous (vasculitis, CTD, pregnancy), aortic dissection with retrograde extension (usually involving RCA → IMI) or mechanical (PCI, surgery, trauma)
  - Embolism (*Circ* 2015;132:241): AF, thrombus/myxoma, endocard., prosth. valve thrombosis
  - Vasculitis: Kawasaki syndrome, Takayasu arteritis, PAN, EGPA, SLE, RA
  - Congenital: anomalous origin from aorta or PA, myocardial bridge (intramural segment)
- **Direct myocardial injury:** myocarditis, Takotsubo/stress CMP, toxic CMP, cardiac contusion

Clinical manifestations (*JAMA* 2015;314:1955)

- **Cardiac chest pain ("angina"):** retrosternal pressure/pain/tightness ± radiation to neck, jaw, arms. Precipitated by exertion (physical or emotional), ↓ w/ rest or NTG. In ACS: new-onset, crescendo, or at rest.
- **Associated symptoms:** dyspnea, diaphoresis, N/V, palpitations or light-headedness
- Nonclassic sx (incl N/V & epig pain) may be more common in ♀, elderly, DM, IMI

Physical exam (signs may be seen, but often are not)

- Signs of ischemia: S_4, new MR murmur 2° pap. muscle dysfxn, paradoxical S_2, diaphoresis
- Signs of HF (eg, if large MI or ischemic MR): ↑ JVP, crackles, ⊕ S_3, HoTN, cool extremities
- Signs of other vascular disease: asymmetric BP, carotid or femoral bruits, ↓ distal pulses

Diagnostic studies (*NEJM* 2017;376:2053)

- **ECG:** ST ↓/↑, TWI, new LBBB, hyperacute Tw; Qw/PRWP may suggest prior MI & ∴ CAD
  ✓ ECG w/in 10 min of presentation, with any Δ in sx & at 6–12 h; compare w/ baseline
- STEMI dx challenging w/ old LBBB or ventricular pacing:
  - Sgarbossa: ≥1 mm STE *concordant* w/ QRS (Se 73%, Sp 92%), STD ≥1 mm V_1–V_3 (Se 25%, Sp 96%), STE ≥5 mm *discordant* w/ QRS (Se 31%, Sp 92%)
  - Barcelona: ST deviation ≥1 mm *concordant* w/ QRS in any lead, or ST deviation ≥1 mm *discordant* w/ QRS in leads with max voltage (largest R or S) ≤6 mm (Se 93%, Sp 94%)

Localization of MI		
Anatomic Area	**ECG Leads w/ STE**	**Coronary Artery**
Septal	V_1–V_2	Proximal LAD
Anterior	V_3–V_4	LAD
Apical	V_5–V_6	Distal LAD, LCx, or RCA
Lateral	I, aVL	LCx
Inferior	II, III, aVF	RCA (~85%), LCx (~15%)
RV	V_1–V_2 & V_4R (most Se)	Proximal RCA
Posterior	ST *depression* V_1–V_3 (= STE V_7–V_9 posterior leads, ✓ if clinical suspicion)	RCA or LCx

If ECG non-dx & suspicion high, ✓ leads V_7–V_9 (⊕ if ≥0.5 mm STE) to assess distal LCx/RCA territory. ✓ R-sided precordial leads in IMI to detect RV involvement (STE in V_4R most Se). STE in III > STE in II and lack of STE in I or aVL suggest RCA rather than LCx culprit in IMI. STE in aVR suggests LM, prox LAD, or diffuse ischemia.

- **Cardiac biomarkers:** ✓ Tn (pref. over CK-MB) at presentation & 3–6 h if conventional assay or 1–2 h later if high-sens assay; repeat if clinical or ECG Δs. **Universal def. of MI:** >99th %ile w/ rise and/or fall in appropriate clinical setting (eg, sx, ECG Δs, WMA).
- If low prob, **stress test** or **CCTA** to r/o CAD; new WMA on TTE suggests ACS
- **Invasive coronary angio** gold standard for epicardial CAD

Prinzmetal's (variant) angina

- Coronary spasm → transient STE usually w/o MI (*but* MI, AVB, VT can occur)
- Pts usually young, smokers, ± other vasospastic disorders (eg, migraines, Raynaud's)
- Angiography: nonobstructive CAD (spasm can be provoked during cath but rarely done)
- Treatment: high-dose CCB & standing nitrates (+SL prn), ? α-blockers/statins; d/c smoking. Avoid: high-dose ASA (can inhibit prostacyclin & worsen spasm), nonselect βB, triptans.
- Cocaine-induced vasospasm: CCB, nitrates, ASA; ? avoid βB, but labetalol appears safe

MI in absence of obstructive CAD (MINOCA)

- Definition: MI but w/o coronary stenosis ≥50% in any major epicardial vessel
- More common in younger Pts, women (2× ♀ > ♂), Black/Pacific race or Hispanic
- Advanced coronary imaging (eg, OCT) & cardiac MRI to exclude missed coronary obstruction, other causes of myocyte injury (eg, myocarditis), other causes of ↑ Tn (eg, PE)
- ~75% ischemic (eg, plaque disruption, SCAD, spasm), 25% alternative dx (eg, myocarditis)

Likelihood of ACS (*Circ* 2007;116:e148; *Circ* 1994;90[1]:613-622)			
Feature	**High** (any of below)	**Intermediate** (no high features, any of below)	**Low** (no high/inter. features, may have below)
History	Chest or L arm pain like prior angina, h/o CAD (incl MI)	Chest or arm pain, age >70 y, male, diabetes	Atypical sx (eg, pleuritic, sharp, or positional pain)
Exam	HoTN, diaphoresis, HF, transient MR	PAD or cerebrovascular disease	Pain reproduced on palp.
ECG	New STD (≥1 mm) TWI in mult leads	Old Qw, STD (0.5–0.9 mm), TWI (>1 mm)	TWF/TWI (<1 mm) in leads w/ dominant R wave
Biomarkers	⊕ Tn or CK-MB	Normal	Normal

Acute Anti-Ischemic and Analgesic Treatment for All ACS Types	
Nitrates (SL or IV) 0.3–0.4 mg SL q5min ×3, then consider IV if still sx	Use for sx, control HTN or Rx of HF. No clear ↓ in mortality. *Caution* if preload-sensitive (eg, HoTN, AS, sx RV infarct); contraindic. if marked brady/tachy or recent PDE5i use.
β-Blockers eg, metop 25–50 mg PO q6h titrate slowly to HR 50–60 *may* consider IV (5 mg q2–5′ × 3) if planning 1° PCI or HTN and no contraindic.	↓ ischemia & progression of UA to MI (*JAMA* 1988;260:2259) STEMI: ↓ arrhythmic death & reMI, but high doses can ↑ cardiogenic shock (espec if signs of HF), & ∴ no Δ overall mortality (*Lancet* 2005;366:1622) *Contraindicated* if PR >0.24 sec, HR <60, 2°/3° AVB, severe bronchospasm, s/s HF or low output, risk factors for shock (eg, >70 y, HR >110, SBP <120, late presentation STEMI)
Morphine	Relieves pain/anxiety; venodilation ↓ preload. Do not mask refractory sx. May delay antiplt effect of $P2Y_{12}$ inhibitor.
Oxygen	Use if needed to keep S_aO_2 >90% (*NEJM* 2017;377:1240)
Transfusion	Data mixed (favoring restrictive in 1 trial, liberal in another, w/ no

	benefit in most anemic in the latter). Hb goal of ≥8 g/dL, can consider ≥10 g/dL (*JAMA* 2021;325:552; *NEJM* 2023;389:2446).

Other early adjunctive therapy for all ACS types

- **Intensive lipid-lowering therapy** High-intensity statin (eg, atorva 80 mg qd) ↓ ischemic events (PROVE-IT TIMI 22, *NEJM* 2004;350:1495) w/ benefit emerging w/in wks (*JAMA* 2001;285:1711 & *JACC* 2005;46:1405); ↓ peri-PCI MI (*JACC* 2010;56:1099); ? ↓ contrast-induced nephropathy (*NEJM* 2019;380:2156)
  - Ezetimibe: ↓ CV events when added to statin (IMPROVE-IT, *NEJM* 2015;372:2387)
  - PCSK9i: being studied in ACS, but favorable effects on plaque & ↓ MACE longterm
- **RASi & MRA:** start once hemodynamics and renal fxn stable (hold RASi if anticipate CABG). See "Long-Term Post-ACS Mgmt" section for details.
- IABP: can be used for refractory angina as bridge to definitive revascularization

NSTE-ACS (*EHJ* 2021;42:1289; *Circ* 2025;151:e771)

Antiplatelet Therapy	
Aspirin: 162–325 mg × 1, then 81 mg qd (non-enteric-coated, chewable)	50–70% ↓ D/MI (*NEJM* 1988;319:1105) If allergy, use clopi and/or desensitize to ASA
$P2Y_{12}$ inhibitor (choose one in addition to ASA). Timing (on presentation or at angio) controversial, but consider upstream clopidogrel or ticagrelor if anticipate >24 hrs to angio.	
• **Ticagrelor** (preferred over clopi) 180 mg × 1 → 90 mg bid Reversible, but wait 3–5 d prior to surg. Antidote being developed (*NEJM* 2019;380:1825).	More rapid and potent plt inhib c/w clopi 16% ↓ CVD/MI/stroke & 21% ↓ CV death c/w clopi; ↑ non-CABG bleeding (*NEJM* 2009;361:1045) Given upstream or at time of PCI Dyspnea (but S_aO_2 & PFTs nl) & ventricular pauses
• **Prasugrel** (preferred over clopi) 60 mg × 1 at PCI → 10 mg qd (consider 5 mg/d if <60 kg) Wait 7 d prior to surgery Contraindicated if h/o TIA/CVA; caution if ≥75 y	More rapid and potent plt inhib c/w clopi 19% ↓ CVD/MI/stroke in ACS w/ planned PCI vs. clopi, but ↑ bleeding (*NEJM* 2007;359:2001) In NSTE-ACS, should be given at time of PCI (not upstream) due to ↑ bleeding (*NEJM* 2013;369:999) ? ↓ MACE vs. ticagrelor (*NEJM* 2019;381:1524)
• **Clopidogrel** 300–600 mg × 1 → 75 mg qd Wait 5 d prior to surgery	ASA+clopi → 20% ↓ CVD/MI/stroke vs. ASA alone ~30% of population has ↓ fxn CYP2C19 → ↑ CV events if PCI on clopi (*NEJM* 2009;360:354)
• **Cangrelor*** Only IV $P2Y_{12}$ inhibitor Rapid onset/offset; t½ 3–5	22% ↓ CV events (mostly peri-PCI MI and stent thrombosis) vs. clopi 300 mg at time of PCI; no significant ↑ bleeding (*NEJM* 2013;368:1303)

min	
GP IIb/IIIa inhibitors (GPI): abciximab; eptifibatide; tirofiban Given ≤24 h peri- & post-PCI	No clear benefit for routinely starting prior to PCI and ↑ bleeding (*NEJM* 2009;360:2176) Consider if large clot burden, no reflow or slow flow

*Transition from cangrelor to oral $P2Y_{12}$ inhib.: ticagrelor loading dose during infusion or immediately after d/c of infusion; prasugrel or clopidogrel loading dose only immediately *after* d/c of infusion

Anticoagulant Therapy (choose one)	
UFH: 60 U/kg IVB (max 4000 U) then 12 U/kg/h (max 1000 U/h initially) × 48 h or until end of PCI	24% ↓ D/MI (*JAMA* 1996;276:811) Titrate to aPTT 1.5–2× control (~50–70 sec) Hold until INR <2 if already on warfarin
Enoxaparin (low-molec-wt heparin) 1 mg/kg SC bid (± 30 mg IVB) (qd if CrCl <30) × 2–8 d or until PCI	~10% ↓ D/MI vs. UFH (*JAMA* 2004;292:45,89). Can perform PCI on enox (*Circ* 2001;103:658), but ↑ bleeding if switch b/w enox and UFH.
Bivalirudin (direct thrombin inhibitor) 0.75 mg/kg IVB at PCI → 1.75 mg/kg/h	No diff in bleeding, MI, or death c/w UFH (*NEJM* 2017;377:1132). Use instead of UFH if HIT.
Fondaparinux (Xa inh) 2.5 mg SC qd	Rarely used; must supplement w/ UFH if PCI

Coronary angiography (*Circ* 2025;141:e00; *EHJ* 2023;44:3720)

- **Immediate/urgent coronary angiography** (w/in 2 h) if refractory/recurrent angina, hemodynamic or electrical instability, s/s HF or cardiogenic shock
- **Invasive strategy**
  - *Routine = coronary angiography for all*
  - *Selective = invasive angio only if recurrent sx or ⊕ noninvasive test (stress or CCTA)*
  - Routine strategy → 32% ↓ rehosp for ACS, nonsignif 16% ↓ MI, no Δ in mort. c/w select angio (*JAMA* 2008;300:71). ↑ peri-PCI MI counterbalanced by ↓↓ in spont. MI.
  - ∴ Routine invasive recommended if high or intermediate risk (eg, based on TIMI or GRACE risk score). If lower risk (TIMI Risk Score <2, GRACE <109, sx resolved, Tn ⊖, no ST Δs) either strategy acceptable.
  - Elderly (≥75): no clear benefit, but 25% ↓ MI; proc. complic. <1% (*NEJM* 2024;391:1673)
- **Timing of angiography** (*NEJM* 2009;360:2165; *Circ* 2018;138:2741)
  - *Early (w/in 24 h) if:* steeply rising Tn, ongoing dynamic ST Δ, GRACE risk score >140
  - *Delayed (ie, w/in 48–72 h) acceptable if:* GRACE 109–140, stable or ↓ Tn, sx resolved
- PCI of all significant non-culprit lesions (either at time of procedure or later during hosp.) ↓ CV death & recurrent MI (*NEJM* 2023;389:889; *JACC* 2024;84:276)

TIMI Risk Score (TRS) for UA/NSTEMI (*JAMA* 2000;284:835)			
Calculation of Risk Score		**Application of Risk Score**	
Characteristic	**Point**	**Score**	**D/MI/UR by 14 d**
Historical		0–1	5%
Age ≥65 y	1	2	8%
≥3 risk factors for CAD	1	3	13%
Known CAD (stenosis ≥50%)	1	4	20%
ASA use in past 7 d	1	5	26%

Presentation		6–7	41%
Severe angina (≥2 episodes w/in 24 h)	1	Higher risk Pts (TRS ≥3) derive ↑ benefit from LMWH, GP IIb/IIIa inhibitors, and early angiography (*JACC* 2003;41:89S)	
ST deviation ≥0.5 mm	1		
⊕ cardiac marker (troponin, CK-MB)	1		
RISK SCORE = Total points	**(0–7)**		

STEMI (*EHJ* 2023;44:3720; *Circ* 2025;151:e771)

Requisite ECG changes

- STE at J point in ≥2 contiguous leads w/ ≥1 mm (except for V_2–V_3: ≥2.5 mm in ♂ <40 yrs, ≥2 mm in ♂ ≥40 yrs, and ≥1.5 mm in ♀ regardless of age), *or*
- New or presumed new LBBB w/ compelling H&P, *or*
- True posterior MI: ST depression V_1–V_3 ± tall Rw w/ STE on posterior leads (V_7–V_9)

Reperfusion ("time is muscle")

- In PCI-capable hospital, goal should be **primary PCI w/in 90 min** of 1st medical contact
- In non–PCI-capable hospital, consider *transfer* to PCI-capable hospital (if PCI w/in 120 min of 1st medical contact), otherwise **fibrinolytic therapy** w/in 30 min of hospital presentation
- Do not let decision regarding *method* of reperfusion delay *time* to reperfusion

Primary PCI (*JACC* 2013;61:e78 & 2016;67:1235)

- Definition: immediate PCI upon arrival to hospital or transfer for immediate PCI
- Indications: **STE** + sx onset w/in <12 h; ongoing ischemia 12–24 h after sx onset; shock
- Superior to lysis: 27% ↓ death, 65% ↓ reMI, 54% ↓ stroke, 95% ↓ ICH (*Lancet* 2003;361:13)
- Transfer to center for 1° PCI superior to lysis (*NEJM* 2003;349:733), vide infra

Fibrinolysis (TNK-tPA, tPA, rPA)

- Indic: STE/LBBB + sx <12 h (& >120 min before PCI can be done); benefit if sx >12 h less clear; reasonable if persist. sx & STE, hemodynamic instability or large territory at risk
- Mortality ↓ ~20% in anterior MI or LBBB and ~10% in IMI c/w Ø reperfusion Rx
- Prehospital lysis (ie, ambulance): further 17% ↓ in mortality (*JAMA* 2000;283:2686)
- ~1% risk of ICH; high risk incl elderly (~2% if >75 y), ♀, low wt. ? PCI more attractive
- **Absolute contraindications**: prior ICH, intracranial neoplasm/aneurysm/AVM, ischemic stroke or closed head trauma w/in 3 mo, head/spinal surg w/in 2 mo, active internal bleed, bleeding diathesis, suspected Ao dissection, severe uncontrolled HTN
- **Relative contraindication**: h/o severe HTN or SBP >180 or DBP >110 on presentation, ischemic stroke >3 mo prior, CPR >10 mins, major surg/trauma w/in 3 wk, internal bleed w/in 2–4 wk, active PUD, pregnancy, current a/c Rx, non-compressible vascular puncture

Nonprimary PCI

- Rescue PCI if shock, unstable, failed reperfusion, or persistent sx (*NEJM* 2005;353:2758)
- Routine angio ± PCI w/in 24 h of successful lysis: ↓ D/MI/revasc (*Lancet* 2004;364:1045) and w/in 6 h ↓ reMI, recurrent ischemia, & HF compared to w/in 2 wk (*NEJM* 2009;360:2705);

∴ *if lysed at hosp. w/o PCI, transfer to PCI-capable hosp. ASAP espec. if high risk (eg, ant. MI, IMI w/ ↓ EF or RV infarct, extensive STE/LBBB, HF, ↓ BP or ↑ HR)*

- Late PCI (median day 8) of occluded infarct-related artery: no benefit (*NEJM* 2006;355:2395)

Antiplatelet Therapy	
Aspirin 162–325 mg × 1 (crushed/chewed) then 81 mg qd	23% ↓ in death (*Lancet* 1988;ii:349) Should not be stopped if CABG required
P2Y$_{12}$ inhibitor *Give ASAP (do not wait for angio)* Ticagrelor or prasugrel (if PCI) as detailed above Clopidogrel: 600 mg pre-PCI; 300 mg if lysis (no LD if >75 y) → 75 mg qd	*PCI:* prasugrel and ticagrelor ↓ CV events c/w clopi (*Lancet* 2009;373:723 & *Circ* 2010;122:2131) Prehospital ticagrelor may be safe & ? ↓ rate of stent thrombosis (*NEJM* 2014;371:1016) *Lysis:* clopidogrel 41% ↑ in patency, 7% ↓ mort, no Δ major bleed or ICH (*NEJM* 2005;352:1179; *Lancet* 2005;366:1607); no data for pras or ticag w/ lytic
GP IIb/IIIa inhibitors abciximab, eptifibatide, tirofiban	*Peri-PCI:* consider if lg thrombus, no/slow reflow *Lysis:* no indication (*Lancet* 2001;357:1905)

(*NEJM* 2021;384:452; *JAMA* 2021;325:1545)

Anticoagulant Therapy (choose one)	
UFH *PCI:* 70–100 U/kg IVB (if w/o GP inhib) *Lysis:* 60 U/kg IVB (max 4000 U) → 12 U/kg/h (max 1000 U/h initially)	No demonstrated mortality benefit ↑ patency with fibrin-specific lytics Titrate to ACT for PCI or to aPTT 1.5–2× control (~50–70 sec) for lysis
Bivalirudin 0.75 mg/kg IVB → 1.75 mg/kg/hr IV extending 2–4 hrs post-PCI	*PCI:* ↓ bleeding, and w/ post-PCI infusion, no excess in ischemic events, ↓ stent thrombosis, and 25% ↓ mortality vs. UFH (*Lancet* 2022;400:1847)
Enoxaparin *PCI:* 0.5 mg/kg IVB *Lysis:* 30 mg IVB → 1 mg/kg SC bid (adjust for age >75 & CrCl)	*PCI:* ↓ D/MI/revasc and ≈ bleeding vs. UFH (*Lancet* 2011;378:693) *Lysis:* 17% ↓ D/MI w/ ENOX × 7 d vs. UFH × 2 d (*NEJM* 2006;354:1477)

Management of non-culprit arteries (*JACC* 2025;85:19)

- Primary PCI refers to revascularization of infarct-related or “culprit” artery in STEMI
- Pts w/ STEMI often have coexisting atherosclerotic lesions in non–infarct-related coronary arteries. Inflammatory milieu post-STEMI may ↑ risk of further plaque rupture.
- PCI of non-culprit arteries (stenoses ≥70% or FFR ≤0.80 if 50–69%) early after STEMI (during initial PCI, prior to or early after d/c) ↓ recurrent MACE, primarily recurrent MI (COMPLETE, *NEJM* 2019;381:1411 & FIRE, *NEJM* 2023;389:889). For unclear reasons, purely FFR-guided revasc of non-culprit lesions did not show a benefit (*NEJM* 2024;390:1481).
- Comparison of immediate vs. staged (19–45 d later) non-culprit PCI showed immediate ↓ ischemia-driven revasc & periprocedural MI (as hard to dx in setting of STEMI), but no clear effect on spont. MI or cardiac death (MULTISTARS AMI, *NEJM* 2023;389:1368). PCI of non-culprit arteries during same hosp. reasonable (espec. if severe proximal stenosis).
- Risks outweigh benefits (↑ death and renal replacement Rx) in Pts with cardiogenic shock at presentation (CvLPRIT-SHOCK, *NEJM* 2017;377:2419)

CABG in STEMI

- Urgent CABG if coronary anatomy not amenable to PCI, particularly if (1) ongoing ischemia or large area of jeopardized myocardium, or (2) cardiogenic shock or severe HF
- Timing based on hemodynamic stability, ongoing ischemia, and myocardium at risk
- Do not hold ASA, but, if possible, wait several days after last dose of $P2Y_{12}$ inhibitor

LV failure (occurs in ~25%)

- Diurese to achieve PCWP ~14 mmHg → ↓ pulmonary edema, ↓ myocardial O_2 demand
- ↓ Afterload → ↑ stroke volume & CO, ↓ myocardial O_2 demand. Can use IV NTG or nitroprusside (although risk of coronary steal) → short-acting ACEI.
- Inotropes if HF despite diuresis & ↓ afterload; use dobutamine, milrinone or dopamine
- **Cardiogenic shock** (~7%) SBP <90, CI <2.2 L/min/m^2, PCWP >18 mmHg, e/o end-organ dysfunction (eg, ↑ lactate)
  - If not done already, coronary revasc (*NEJM* 1999;341:625)
  - Support w/ inotropes or mechanical circulatory support to keep CI >2.2
    - **Intra-aortic balloon pump (IABP)** counterpulsation offers ~0.5 L/min CO and ↑ coronary perfusion, but no 30-day survival benefit if early revasc or long-term survival benefit (*NEJM* 2012;367:1287; *Circ* 2018;139:395)
    - **Axial flow pumps (eg, Impella)** offer up to 3.7–5.5 L/min CO, ↓ death by 26%, but approximately doubled risk of major bleeding, sepsis, and renal replacement therapy, and ~6% risk of limb ischemia (*NEJM* 2024;390:1382)

IMI complications (*Circ* 1990;81:401; *NEJM* 1994;330:1211; *JACC* 2003;41:1273)

- **Heart block:** ~20%, occurs in part because RCA typically supplies AV node; 40% on present., 20% w/in 24 h, rest by 72 h; high-grade AVB can develop abruptly; Rx: atropine, epi, aminophylline (100 mg/min × 2.5 min), temp pacing wire
- **RV infarct:** proximal RCA occlusion → ↓ flow to RV marginals
  - Angiographically present in 30–50% of cases, but only ~½ clinically significant
  - HoTN, ↑ JVP, ⊕ Kussmaul's; ≥1 mm STE in V_4R; RA/PCWP ≥0.8; RV dysfxn on TTE
  - Rx: optimize preload (RA goal 10–14 mmHg; *BHJ* 1990;63:98); ↑ contractility (dobutamine); maintain AV synchrony (pacing as necessary); reperfusion (*NEJM* 1998;338:933); mechanical support (eg, RVAD); pulmonary vasodilators (eg, inhaled NO)

Mechanical complications (incid. **<1%** for each; typically occur a few days post-MI)

- **Free wall rupture:** ↑ risk w/ lysis, large MI, ↑ age, ♀, HTN; p/w PEA or hypoTN, pericardial sx, tamponade; Rx: volume resusc., ? pericardiocentesis, inotropes, **surgery**
- **VSD:** large MI; AMI → apical VSD, IMI → basal septum; 90% w/ harsh murmur ± thrill (*NEJM* 2002;347:1426); Rx: diuretics, vasodil., inotropes, IABP/MCS, **surgery**, perc. closure
- **Papillary muscle rupture:** more common after IMI (PM pap m. supplied by PDA alone) than AMI (AL pap m. supplied by OMs & diags); 50% w/ new murmur; ↑ *v* wave in PCWP tracing; asymmetric pulm edema. Rx: diuretics, vasodilators, IABP/MCS, **surgery.**

Arrhythmias post-MI (treat all per ACLS protocols if unstable or symptomatic)

- **AF** (10–16% incidence): βB or amio, ± digoxin (particularly if HF), heparin
- **VT/VF:** lido or amio × 6–24 h, then reassess; ↑ βB as tol., replete K & Mg, r/o ischemia; MMVT <48 h post-MI does *not* worsen prognosis; >48 h, consider ICD (vide infra)
- Accelerated idioventricular rhythm (AIVR): "slow VT" (<110 bpm), often after reperfusion; typically asx, gradual onset/offset, and does not require treatment
- Backup transcutaneous *or* transvenous pacing if: 2° AVB type II; BBB + AVB
- **Transvenous pacing** if: 3° AVB; new BBB + 2° AVB type II; alternating LBBB/RBBB

Other Post-MI Complications (*JACC* 2024;83:1886, 1902, 1917)		
Complication	**Clinical Features**	**Treatment**
LV thrombus	~30% incid. (espec lg anteroapical MI)	AC × 3–6 mo (VKA or DOAC)
Ventricular aneurysm	Noncontractile outpouching of LV; 8–15% incid. (espec ant); persist STE	Surgery or perc repair if HF, thromboemboli, arrhythmia
Ventricular pseudoaneurysm	Rupture (narrow neck) → sealed by thrombus and pericardium (esp in inf).	Urgent surgery (or percutaneous repair)
Pericarditis	10–20% incid.; 1–4 d post-MI ⊕ pericardial rub; ECG Δs rare	High-dose ASA, colchicine, Ø NSAIDs; minimize anticoag
Dressler's syndrome	<4% incid.; 2–10 wk post-MI fever, pericarditis, pleuritis	High-dose aspirin, colchicine

Checklist and Long-Term Post-ACS Management

Risk stratification

- Stress test if anatomy undefined
- If significant residual CAD (beyond revascularized culprit lesion) consider revascularization during index hospitalization (vide supra)
- Assess LVEF prior to d/c; EF ↑ ~6% after STEMI over 6 mo (*JACC* 2007;50:149)

Antiplatelet therapy

- **Aspirin:** 81 mg daily (no clear benefit to higher doses)
- **$P2Y_{12}$ inhibitor:** ticagrelor or prasugrel preferred over clopi. In landmark analyses, benefit over clopidogrel both early & late. De-escalation (ticag → clopi or pras 10 → 5 mg) after 1 mo ↓ bleeding w/o clear ↑ MACE, but wide CIs (*Lancet* 2020;396:1079 & 2021;398:1305).
- Duration controversial. Traditionally ASA lifelong and $P2Y_{12}$ inhib for 12 mos. *d/c ASA* after 1–3 mos and continue $P2Y_{12}$ inhib monoRx (pref. ticagrelor, not clopi) ↓ bleeding ~40% w/o ↑ MACE (*Circ* 2020;142:538; *JAMA Cardiol* 2022;7:407; *Lancet* 2024;404:937) *prolonged $P2Y_{12}$ inhib* >12 mos → ↓ MACE but ↑ bleeding (*NEJM* 2014;371:2155 & 2015;372:1791). Consider if high ischemic and low bleeding risk.
- PPI should be started w/ DAPT or AC if high GI bleeding risk

Anticoagulation

- If need a/c (eg, AF), use DOAC + DAPT (typically clopi + ASA) then d/c ASA after 1–4 wks
- Consider dropping $P2Y_{12}$ inhibitor after 6–12 mos depending on bleeding & ischemic risk

Other CV drugs

- **β-blocker:** in older trials, 23% ↓ mortality after MI. Recent open-label trial w/ relatively high crossover did not show benefit of post-discharge βB in AMI s/p revasc w/ nl LVEF (although possible benefit in STEMI) (*NEJM* 2024;390:1372).
- **ACEI/ARB:** if HF, ↓ EF, HTN, DM, anterior STEMI. Trend toward ARNI better than ACEI in post-MI Pts w/ ↓ EF (*NEJM* 2021;385:1845). ? long-term benefit of ACEI/ARB in CAD w/o HF (*NEJM* 2000;342:145 & 2004;351:2058).
- **Aldosterone antag:** 15% ↓ mort. if EF <40% & either s/s of HF or DM (*NEJM* 2003;348:1309); in STEMI Rx'd w/ PPCI, no Δ in mort., but nonsignif. 23% ↓ HF hosp (*NEJM* 2025;392:643)
- Nitrates: standing long-acting agents if symptomatic; SL NTG prn for all
- Mixed data for low-dose colchicine (*NEJM* 2019;381:2497; 2025;392:633)

Risk factors and lifestyle modifications (*Circ* 2019;139:e1082 & 2025;151:e771; *EHJ* 2020;41:111)

- **LDL-C**: goal <55 mg/dL or even <40 mg/dL if recurrent events
  - *Statin*: high-intensity ↓ LDL-C by ~50% & ↓ MACE (PROVE-IT TIMI 22, *NEJM* 2004;350:1495)
  - *Ezetimibe*: ↓ LDL-C by ~20–24% & ↓ MACE when added to statin (IMPROVE-IT, *NEJM* 2015;372:1500)
  - *PCSK9 inhibitor*: ↓ LDL-C by ~60% & ↓ MACE when added to statin (*NEJM* 2017;376:1713; 2018;379:2097)
  - *Bempedoic acid* ↓ LDL-C by ~18% & ↓ MACE in Pts not on statin (*NEJM* 2019;380:3022)
- **BP** <130–140/80–90, ? SBP 120s espec. if DM (*NEJM* 2021;384:1921 & 2025;392:1155)
- DM: GLP-1RA ↓ MACE. SGLT2i ↓ CV death/HF hosp, w/ possible ↓ MI (*Lancet D&E* 2019;7:776; *Circ* 2024;149:1789); further tailor Hb_{A1c} goal based on Pt (avoid TZDs and saxa if HF)
- BMI ≥27: GLP-1RA ~20% ↓ MACE (*NEJM* 2023;389:2221)
- Quit smoking; exercise (30–60′ 5–7×/wk) 1–2 wk after revasc; cardiac rehab (center or home based) ↓ MI and CV mortality (*NEJM* 2024;390:830)
- Influenza vaccine (*Circ* 2021;144:14764; *NEJM* 2018;378:345); ✓ for depression

ICD (*Circ* 2018;138:e272)

- Sustained VT/VF >2 d post-MI w/o reversible ischemia
- 1° prevention if EF 31–40% w/ NYHA II–III or induc. VT or ≤30% w/ NYHA I–III; wait ideally 40 d after MI and 90 d after revasc. ? *Wearable* defib as bridge (*NEJM* 2018;379:1205).

PA CATHETER AND TAILORED THERAPY

Rationale

- Cardiac output (CO) = SV × HR; optimize SV (and thereby CO) by manipulating preload/ LVEDV (w/ IVF, diuretics), contractility (w/ inotropes), & afterload (w/ vasodilators)
- Balloon at catheter tip inflated → floats into "wedge" position. Column of blood extends from tip of catheter, through pulm venous circulation to a point just prox to LA. Under conditions of no flow, PCWP ≈ LA pressure ≈ LVEDP, which is proportional to LVEDV.
- Situations in which these basic assumptions fail:
  1. Catheter tip not in West lung zone 3 (and ∴ PCWP = alveolar pressure ≠ LA pressure); clues include lack of *a* & *v* waves and if PA diastolic pressure < PCWP
  2. PCWP > LA pressure (eg, mediastinal fibrosis, pulmonary VOD, PV stenosis)
  3. Mean LA pressure > LVEDP (eg, MR, MS)
  4. Poor compliance: "nl" LVEDP may not translate to adequate LVEDV

Indications (*NEJM* 2013;369:e35; *Circ* 2017;136:e268)

- **Diagnosis and evaluation**
  - Ddx of shock (cardiogenic vs. distributive; espec if trial of IVF failed or is high risk) and of pulmonary edema (cardiogenic vs. not; espec if trial of diuretic failed or is high risk)
  - Evaluation of CO, intracardiac shunt, pulm HTN, MR, tamponade, cardiorenal syndrome
  - Evaluation of unexplained dyspnea (PAC during provocation w/ exercise, vasodilator)
- **Therapeutics** (*Circ* 2017;136:e232)
  - Tailored therapy to optimize PCWP, SV, $S_{MV}O_2$, RAP, PVR in heart failure or shock
  - Guide to vasodilator therapy (eg, inhaled NO, nifedipine) in PHT, RV infarction
  - Guide peri-op mgmt in some high-risk Pts, candidacy for mech circ support & transplant
- **Contraindications**

Absolute: right-sided endocarditis, thrombus/mass or mechanical valve; proximal PE
Relative: coagulopathy (reverse), recent PPM or ICD (place under fluoroscopy), LBBB (~5% risk of RBBB → CHB, place under fluoro), bioprosthetic R-sided valve

Efficacy concerns (*NEJM* 2006;354:2213; *JAMA* 2005;294:1664)

- No benefit to routine PAC use in high-risk surgery (*JACC* 2014;62:e77), sepsis, ARDS
- No benefit in decompensated HF (*JAMA* 2005;294:1625); untested in cardiogenic shock
- But: ~½ of *clinical* CO & PCWP estimates incorrect; CVP & PCWP not well correl.; ∴ use PAC to (a) answer hemodynamic ? and then remove, or (b) manage cardiogenic shock

Placement (*NEJM* 2013;369:e35)

- Insertion site: **R IJ** or **L subclavian veins** preferred for "anatomic" flotation into PA
- **Inf late** balloon (max 1.5 mL, mindful of resistance) when **advancing** and to ✓ **PCWP**
- **Deflate** the balloon when **withdrawing** and at all other times
- CXR should be obtained after placement to assess for catheter position and PTX
- If catheter cannot be floated (ie, severe TR, RV dilatation), consider fluoroscopic guidance

Complications

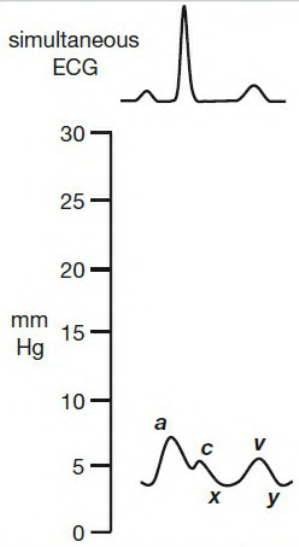
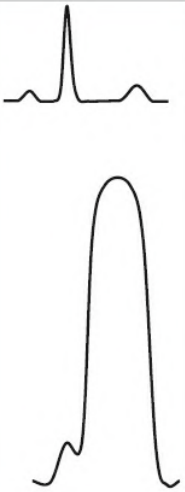
- **Central venous access:** pneumo/hemothorax (~1%), arterial puncture (if inadvertent cannulation w/ dilation → surgical/endovasc eval), air embolism, thoracic duct injury
- **Advancement:** atrial or ventricular arrhythmias (20% NSVT; 3% VT), RBBB (5%), catheter knotting, cardiac perforation/tamponade, PA rupture
- **Maintenance:** infection (espec if catheter >3 d old), thrombus, pulm infarction (≤1%), valve/chordae damage, PA rupture/pseudoaneurysm (espec w/ PHT), balloon rupture

Intracardiac pressures

- Transmural pressure (≈ preload) = measured intracardiac pressure – intrathoracic pressure
- Intrathoracic pressure (usually slightly ⊖) is transmitted to vessels and heart
- **Always measure intracardiac pressure at end-expiration**, when intrathoracic pressure closest to 0 ("high point" in spont. breathing Pts; "low point" in Pts on ⊕ pressure vent.)
- If ↑ intrathoracic pressure (eg, PEEP), measured PCWP *overestimates* true transmural pressures. Can approx by subtracting ~½ PEEP (× ¾ to convert cm H_2O to mmHg).
- PCWP: LV preload best estimated at *a* wave; risk of pulm edema driven by avg PCWP

Cardiac output

- **Thermodilution:** saline injected in RA or intermittent heating of prox thermal filament in some PA lines ("continuous CO"). Δ in temp over time measured at thermistor (in PA) used to calc CO. Inaccurate if ↓ CO, severe TR, or shunt.
- **Fick method:** O_2 consumption (L/min) = CO (L/min) × Δ arteriovenous O_2 content ∴ **CO=$\dot{V}O_2$/C(a–v)O_2**
  - $\dot{V}O_2$ ideally measured (esp. if ↑ metab demands), but freq estimated (125 mL/min/m^2)
  - $C(a\text{-}v)O_2$ = [10 × 1.36 mL O_2/g of Hb × Hb g/dL × (S_aO_2 – $S_{MV}O_2$)]. *$S_{MV}O_2$ is key var that* Δ*s.*
  - If $S_{MV}O_2$ >80%, consider if PAC is "wedged" (ie, pulm vein sat), L→R shunt, impaired O_2 utilization (severe sepsis, cyanide, carbon monoxide), ↑↑ CO or FiO_2

PA Catheter Waveforms				
Location	**RA**	**RV**	**PA**	**PCWP**
Distance	~20 cm	~30 cm	~40 cm	~50 cm
Normal pressure (mmHg)	mean ≤6	syst 15–30 diast 1–8	syst 15–30 mean 9–18 diast 6–12	mean ≥12
Waves				
Comment	*a* = atrial contraction, occurs in PR interval *c* = bulging TV back into RA at start of systole *x* = atrial relax and descent of base of heart *v* = blood entering RA, occurs mid T wave *y* = blood exiting RA after TV opens at start of diastole	RVEDP occurs right before upstroke and ≥ mean RA pressure unless there is TS or TR	Waveform should contain notch (closure of PV). Peak *during* Tw. PA systolic = RV systolic unless there is PS. PA diastolic ≈ PCWP unless ↑ trans-pulm ∇ (eg, ↑ PVR).	Similar to RA except *dampened* and *delayed*. *a* wave *after* QRS, ± distinct *c* wave, *v* wave *after* Tw (helps distinguish PCWP w/ large *v* waves 2° MR from PA).

- PCWP waveform abnormalities: large *a* wave → ? mitral stenosis; large *v* wave → ? mitral regurgitation; blunted *y* descent → ? tamponade; steep *x* & *y* descents → ? constriction

Other calculated metrics

- **SVR & PVR:** calculated by applying Ohm's law (V = IR, or voltage = current × resistance) to circulation. SVR = (MAP – RAP) / CO. PVR = (mean PA pressure – PCWP) / CO.
- Pulmonary artery pulsatility index (PAPi): measure of RV f**x**n based on ratio of R-sided pulse pressure to filling pressure where PAPi = [PA systolic – PA diastolic] / RA pressure

Hemodynamic Profiles of Various Forms of Shock (*NEJM* 2013;369:1726)				
Type of Shock	**RA**	**PCWP**	**CO**	**SVR**
Hypovolemic	↓	↓	↓	↑
Cardiogenic	nl or ↑	↑	↓	↑

RV infarct/massive PE	↑	nl or ↓	↓	↑
Tamponade	↑	↑	↓	↑
Distributive	variable	variable	usually ↑ (can be ↓ in sepsis)	↓

Surrogates: RA ≈ JVP (1 mmHg = 1.36 cm H_2O); pulmonary edema on CXR implies ↑ PCWP; UOP ∝ CO (barring AKI); delayed capillary refill (ie, >2–3 sec) implies ↑ SVR

Tailored therapy in cardiogenic shock (*Circ* 2009;119:e391)

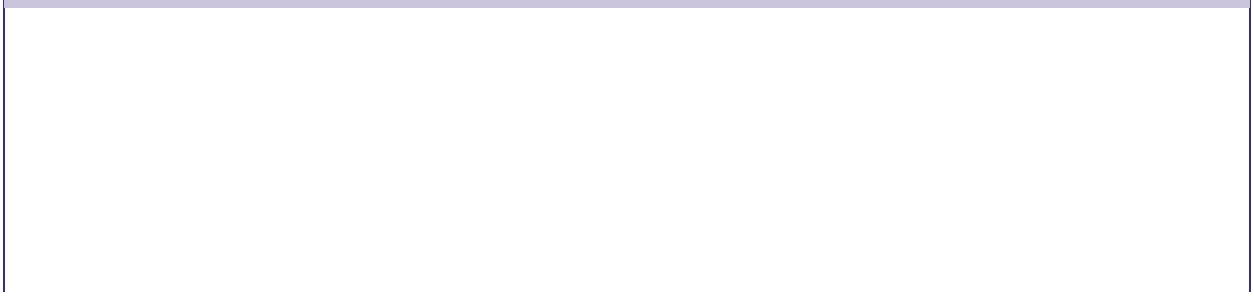
- **Goals:** optimize both MAP and CO while ↓ risk of pulmonary edema
  MAP = CO × SVR; CO = HR × SV (which depends on preload, afterload, and contractility)
  pulmonary edema when PCWP >20–25 (↑ levels may be tolerated in chronic HF/MS)
  hepatic and renal congestion (↓ GFR) occur when CVP/RAP >15 mmHg
- **Optimize preload** = LVEDV ≈ LVEDP ≈ LAP ≈ PCWP (*NEJM* 1973;289:1263)
  goal **PCWP ~14–18 in acute MI, ≤14 in acute decompensated HF**
  optimize in individual Pt by measuring SV w/ different PCWP to create Starling curve
  ↑ by giving crystalloid (albumin w/o clinical benefit over NS; PRBC if significant anemia)
  ↓ by diuresis (qv), continuous hemofiltration if refractory to diuretics or ESRD
- **Optimize afterload** ≈ wall stress during LV ejection = [(~SBP × radius) / (2 × wall thick.)] and **∴** ∝ MAP and ∝ SVR; goals: **MAP** >**60**, **SVR 800–1200**
  MAP >60 (& **∴** SVR ↑): vasodilators (eg, nitroprusside, NTG, ACEI, hydral.) or wean pressors
  MAP <60 (& **∴** SVR low/nl, ie, inappropriate vasoplegia): start with inopressor
- **Optimize contractility** ∝ CO for given preload & afterload; **goal CI** = **(CO / BSA)** >**2.2** if too low despite optimal preload & vasodilators (as MAP permits):
  ⊕ *inotropes:* eg, dobutamine (mod inotrope & mild vasodilator) or milrinone (strong inotrope & vasodilator, incl pulm), both proarrhythmic, or epi (strong inotrope & pressor)
  mech circulatory support: Impella (↓ death in STEMI); IABP; VA ECMO

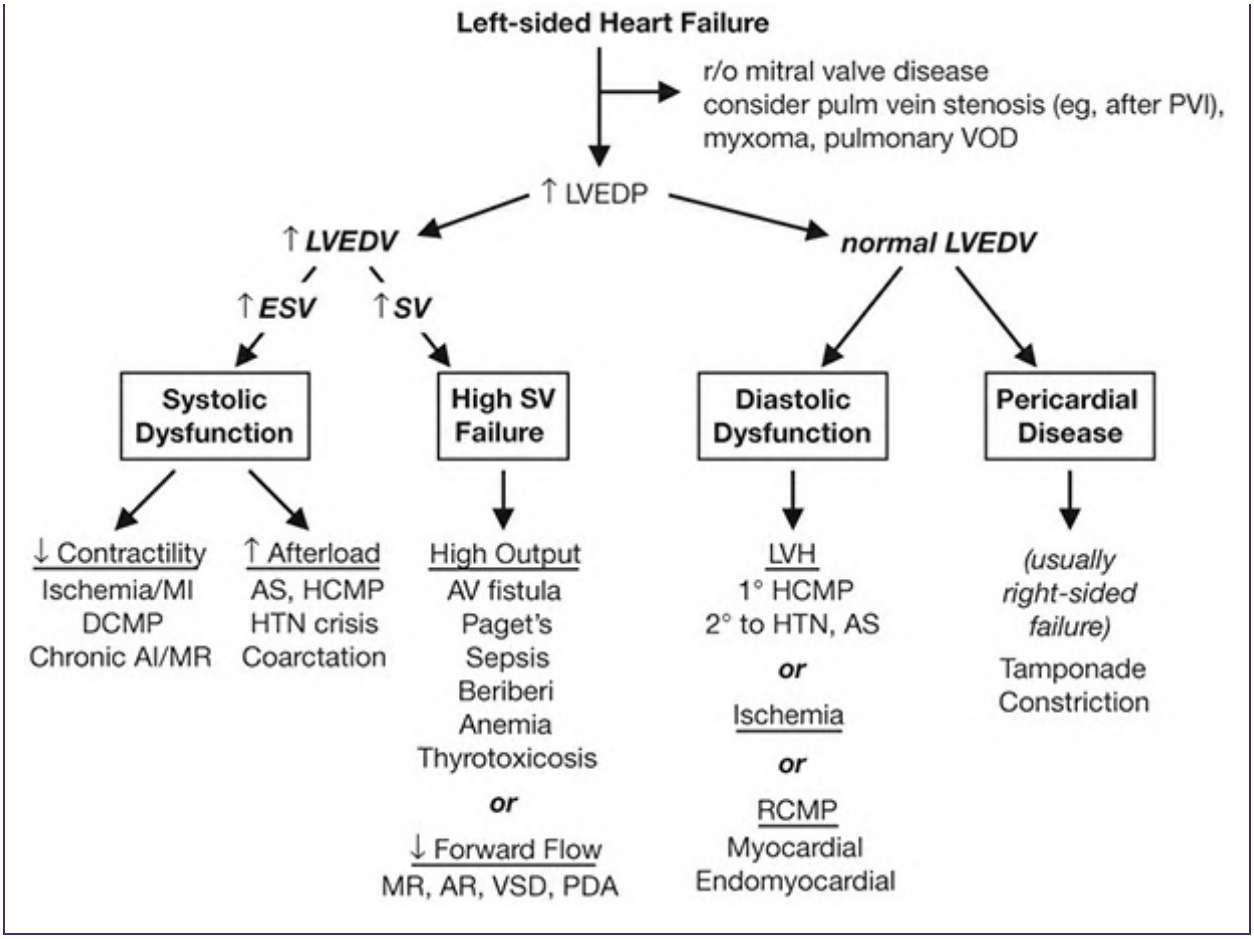
HEART FAILURE

Definitions (*Braunwald's Heart Disease*, 12th ed, 2022; *Circ* 2022;145:e895)

- Failure of heart to pump blood forward at rate sufficient to meet metabolic demands of peripheral tissues, or ability to do so only at abnormally high cardiac filling pressures
- Low output (↓ cardiac output) vs. high output (↑ stroke volume ± ↑ cardiac output)
- Left-sided (pulmonary edema) vs. right-sided (↑ JVP, hepatomegaly, peripheral edema)
- Backward (↑ filling pressures, congestion) vs. forward (impaired systemic perfusion)
- Systolic (inability to expel sufficient blood) vs. diastolic (failure to relax and fill normally)
- Reduced (HFrEF, EF <40%), mildly reduced (HFmrEF, EF 40–49%), preserved (HFpEF, EF >50%), improved (HFimpEF, baseline ≤40%, follow-up >40% & 10% ↑ from baseline)

Figure 1-2 Approach to left-sided heart failure





History

- Low output: fatigue, weakness, exercise intolerance, Δ MS, anorexia, nausea, vomiting
- Congestive: left-sided → dyspnea, orthopnea, paroxysmal nocturnal dyspnea
  right-sided → peripheral edema, RUQ discomfort, bloating, satiety

Functional classification (New York Heart Association class)

- Class I: no sx w/ ordinary activity; class II: sx w/ ordinary activity; class III: sx w/ minimal activity; class IV: sx at rest

Physical exam ("2-minute" hemodynamic profile; *JAMA* 1996;275:630 & 2002;287:628)

- **Congestion ("dry" vs. "wet"):** ↑ JVP (~80% of the time JVP >10 → PCWP >22)
  ⊕ hepatojugular reflux: ≥3 cm ↑ in JVP for ≥10–15 sec w/ abdominal pressure Se/Sp 73/87% for RA >8 and Se/Sp 55/83% for PCWP >15 (*AJC* 1990;66:1002)
  S_3 (in Pts w/ HF → ~40% ↑ risk of HF hosp. or pump failure death; *NEJM* 2001;345:574)
  Rales, dullness at base 2° pleural effus. (*often absent* in chronic HF due to lymphatic compensation) ± hepatomegaly, ascites and jaundice, peripheral edema
- **Perfusion ("warm" vs. "cold")**
  narrow pulse pressure (<25% of SBP) → CI <2.2 (91% Se, 83% Sp; *JAMA* 1989;261:884);
  soft S_1 (↓ dP/dt), pulsus alternans, cool & pale extremities, ↓ UOP, muscle atrophy
- ± Other: Cheyne-Stokes resp., abnl PMI (diffuse, sustained or lifting depending on cause of HF), S_4 (diast. dysfxn), murmur (valvular dis., ↑ MV annulus, displaced papillary muscles)

Evaluation for the presence of heart failure

- CXR (see Radiology insert): pulm edema, pleural effusions ± cardiomegaly, cephalization, Kerley B-lines; lung U/S better than CXR (PPV & NPV 92% vs. 77%; *Chest* 2015;148:202)
- BNP/NT-proBNP can help exclude HF; levels ↑ w/ age, renal dysfxn, AF; ↓ w/ obesity (∴ can be less helpful in HFpEF, which has high rates of obesity); Se ≥95%, Sp: ~50%, PPV ~65%, NPV ≥ 94% for HF in Pts p/w SOB (*BMJ* 2015;350:h910)
- Evidence of ↓ organ perfusion: ↑ Cr, ↓ Na, abnl LFTs, ↑ lactate
- Echo (see inserts): ↓ EF & ↑ chamber size → systolic dysfxn; hypertrophy, abnl MV inflow, abnl tissue Doppler → ? diastolic dysfxn; abnl valves or pericardium; ↑ estimated RVSP
- PA catheterization: ↑ PCWP, ↑ CVP, ↓ CO, and ↑ SVR (in low-output failure)

Evaluation for the potential causes of heart failure

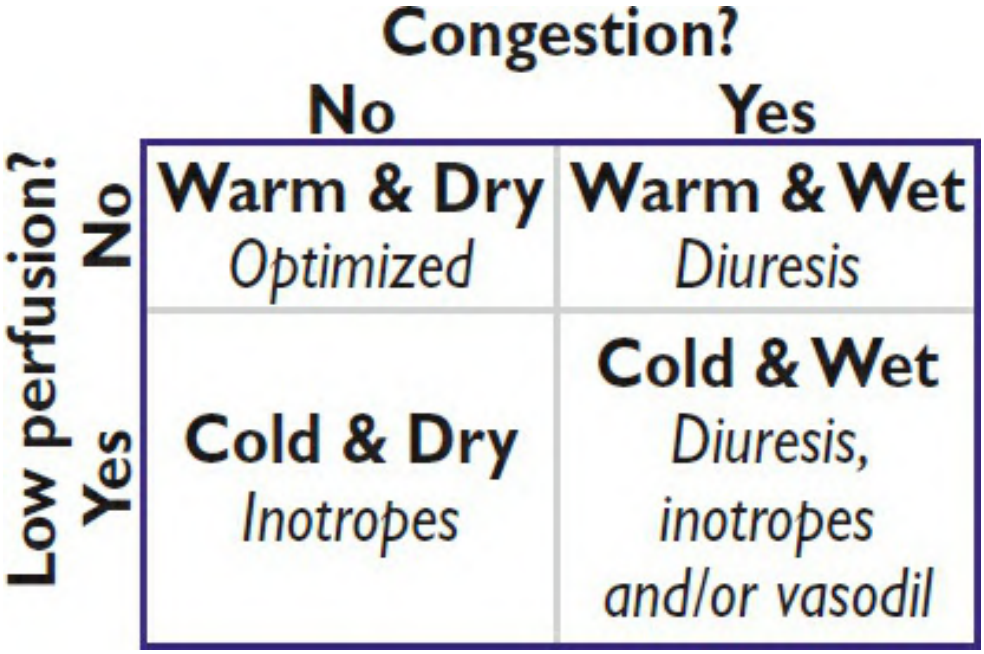
- **ECG:** e/o CAD, LVH, LAE, arrhythmia, heart block, or low voltage (? infiltrative CMP/DCM)
- **TTE:** LV & RV size & fxn, valve abnl (cause or consequence?), infiltrative or pericardial dis.
- **Cardiac MRI:** distinguishes ischemic vs. nonischemic and can help determine etiol. of latter
- **Coronary angio** (or noninv. imaging, eg, CT angio, or stress); if no CAD, w/u for NICM

Precipitants of acute heart failure

- **Dietary indiscretion or medical nonadherence** (~40% of cases)
- **Myocardial ischemia or infarction** (~10–15% of cases); **myocarditis**
- **Renal failure** (acute, progression of CKD, or insufficient dialysis) → ↑ preload
- **Hypertensive crisis (incl. from RAS), worsening AS** → ↑ left-sided afterload
- **Drugs** (βB, CCB, NSAIDs, TZDs), **chemo** (anthracyclines, trastuzumab), or **toxins** (EtOH)
- **Arrhythmias; acute valvular dysfxn** (eg, endocarditis), espec mitral or aortic regurgitation
- COPD/PE → ↑ right-sided afterload; extreme stress; anemia; systemic infxn; thyroid dis.

Rx of acute decompensated HF

- Assess congestion & adequacy of perfusion
- For **congestion:** IV loop diuretics (1–2.5× usual total PO dose) ± thiazides or acetazolamide (*NEJM* 2022;387:1185); no clear Δ between gtt vs. IVB q12h; oral bioavailability ~50% for furosemide (so IV 2× as potent as PO), 80–100% for torsemide. Consider nitrates, especially if HTN.
- "LMNOP": **L**asix, **M**orphine (↓ sx & preload), **N**itrates (↓ preload), **O**xygen (± NIV), **P**osition (sitting up & legs dangling → ↓ preload)
- For **low perfusion**, vide infra
- **Home meds:** prefer to continue, except:
  RASi: hold/↓ dose if HoTN; Δ to hydral/nitrates w/ AKI
  βB: hold if hypoperfusion or HoTN



Treatment of acute advanced heart failure (*Circ* 2013;128:e240)

- Consider PAC if not resp to Rx, unsure re: vol status, HoTN, hypoperfusion, need inotropes
- Tailored Rx w/ PAC (qv); goals of MAP >60, CI >2.2 (MVO2 >60%), SVR ~1000, PCWP <18
- **IV vasodilators:** nitroprusside (preferred due to potent ↓ in SVR; risk of coronary steal if CAD), NTG (venodilation > arterial dilation; eventual tachyphylaxis)
- **Inotropes** (properties in addition to ↑ inotropy and arrhythmogenicity listed below)
  dobutamine: vasodilation at ≤5 µg/kg/min; mild ↓ PVR; desensitization; lasts mins
  dopamine: splanchnic vasodil. → ↑ GFR & natriuresis; vasoconstrictor at ≥5 µg/kg/min
  milrinone: ↑↑ systemic/pulmonary vasodilation; ↓ dose by 50% in renal dysfxn; lasts hours
- **Mechanical circulatory support** (also see "Tailored Therapy" *JACC* 2015;65:e7 & 2542)
  Temporary: bridge to recovery, transplant, or durable MCS; periprocedural support Intra-aortic balloon pump (IABP): inflates in diastole & deflates in systole to ↓ impedance to LV ejection, ↓ myocardial O_2 demand & ↑ coronary perfusion; +0.5 L/min CO Axial flow pumps (eg, Impella): Archimedes screw principle in LV; +3.7–5.5 L/min Extracorporeal centrifugal pumps: CentriMag (10 L/min, but typically 5–7; surgical) Extracorporeal membrane oxygenation (ECMO): 6 L/min (*JACC HF* 2018;6:503)
  Durable: surgically placed LVAD ± RVAD as bridge to sufficient recovery (in 5–50% of niCMP; *JACC* 2017;69:1924), to transplant or as destination Rx (>50% ↓ 1-y mort. vs. med Rx; *NEJM* 2001;345:1435 & 2009;361:2241). Most common option is fully magnetically levitated centrifugal flow pump (HeartMate 3), axial flow models and HeartWare devices taken off the market (*NEJM* 2019;380:1618; *JAMA* 2022;328:1233).
- Cardiac transplantation: ~4500/yr in U.S. <10% mort. in 1st y, median survival >12 y

Recommended Chronic Therapy by HF Stage (*JACC* 2021;77:772)		
Stage (not NYHA Class)		**Therapy**
A	At risk for HF (eg, HTN); but asx & w/o struct. dis.	Rx HTN, lipids, DM; stop smoking, EtOH; ↑ exercise ACEI/ARB if HTN/DM/CAD/PAD
B	⊕ Struct. heart dis. (eg, CMP, LVH), but asx	As per stage A + ACEI/ARB + βB if MI/CAD or ↓ EF. ? ICD.
C	⊕ Struct. heart dis.	As per stage A + diuretics, ↓ Na

	⊕ Any h/o sx of HF	If rEF: RASi (ARNI > ACEI/ARB); βB; MRA; SGLT2i; ICD; ? CRT; ± nitrate/hydral; ± dig If pEF: ?ARNI; MRA; SGLT2i; GLP-1RA if BMI >30
D	Refractory HF requiring specialized interventions	All measures for stages A–C. Consider IV inotropes, VAD, transplant, end-of-life care (4-y mortality >50%).

- Implantable PA pressure sensor in sx Pts: ~30% ↓ risk of hosp (*Lancet* 2016;387:453; 2021;398:991; 2023;401:2113); possibly ↓ mortality in HFrEF w/ prior HF hosp (JACC 2024;83:682)

Treatment of Chronic HF with Reduced EF (*EHJ* 2021;42:3599; *Circ* 2022;145:e895)	
Diuretics	Loop ± thiazides diuretics (sx relief; no mortality benefit)
RASi: ARNI (ARB + neprilysin inhib), **ACEI,** or **ARB** 36-hr washout if transition ACEI to ARNI; N/A for ARB	*ARNI preferred*. Neprilysin degrades natriuretic peptides, bradykinin & ATII. Valsartan + sacubitril ↓ CV mort & HF hosp by 20% vs. ARB; ↑ HoTN, AKI (*NEJM* 2014;371:993). ∅ if h/o angioedema. *ACEI or ARB:* if unable to tolerate/afford ARNI. ↓ mortality vs. pbo. High-dose more effective. Watch for ↑ Cr, ↑ K (Rx: low-K diet, diuretics, K binders), cough (ACEI), angioedema.
β-blocker (data for carvedilol, metoprolol, bisoprolol)	*Add in concert w/ RASi* 35–40% ↓ mort. and in HF hosp in NYHA II–IV (*JAMA* 2002;287:883) EF will transiently ↓, then ↑. Contraindicated in ADHF.
Mineralocorticoid receptor antagonists	*Add after RASi and βB if adeq. renal fxn and w/o hyperkalemia* 30–35% ↓ CV mortality & HF hosp in NYHA II–IV (*Lancet* 2024;404:1119) Watch for ↑ K. Do not use if GFR <30 or K ≥5.
SGLT2i	~25% ↓ death or HF hosp in NYHA II–IV *(NEJM* 2019;381:1995; 2020;383:1413; 2021;385:1451). Limited data in eGFR <20. Risk of GU infection, euglycemic DKA.
Hydralazine + nitrates	*Consider if cannot tolerate ACEI/ARB or in Black Pts w/ class III/IV* 25% ↓ mort. but inferior to ACEI (*NEJM* 1991;325:303) 40% ↓ mort. in Blacks on standard Rx (A-HEFT, *NEJM* 2004;351:2049)
Ivabradine (I_f blocker)	*Reasonable if EF ≤35%, NYHA II–III, HR ≥70, NSR on max βB*. ↓ HR w/o ⊖ inotropy. 18% ↓ CV mort or HF hosp (*Lancet* 2010;376:875).
Digoxin	23% ↓ HF hosp., no Δ mort. Optimal levels 0.5–0.8 ng/mL.
Vericiguat	10% ↓ CV mort or HF hosp in NYHA II–IV (*NEJM* 2020;382:1883)
Cardiac resynch therapy (CRT, qv)	*Consider if EF ≤35%, LBBB or IVCD ≥150 ms, and sx HF.* ~40% ↓ mort. & HF hosp (*NEJM* 2005;352:1539 & 2014;370:1694). No clear e/o benefit if QRS <150 ms or RBBB (*Circ* 2023;147:812)
ICD (qv)	*For 1° prevention if EF ≤30–35% or 2° prevention; not if NYHA IV* ↓ mort. in ischemic CMP but perhaps only SCD in modern era in niCMP (*NEJM* 2005;352:225 & 2016;375:1221)
Revasc.	↓ CV mortality w/ CABG but not PCI (*NEJM* 2016;374:1511 & 2022;387:135)
mTEER	*If mod–severe fxnal MR & LVEF ≤30–35% on GDMT* 25–30% ↓ death or HF hosp (*NEJM* 2018;379:2297 & 2307; 2024;391:1799)
Heart rhythm	If AF & NYHA II–IV w/ EF <35%, catheter ablation ↓ D/HF hosp and need for advanced Rx vs. med Rx (*NEJM* 2018;378:417; 2023;389:1380)
Iron supplementation	*IV (not PO) if NYHA II/III, EF ≤40%, Fe-defic* (ferritin <100 or 100–300 & TSAT <20%). ~20% ↓ HF hosp. or CV mortality (*Nature Med* 2025;epub).

Diet, exercise	? Na <2 g/d, ? fluid restriction, exercise training in ambulatory Pts
Meds to avoid	NSAIDs, nondihydropyridine CCB, TZDs

Heart Failure with Preserved EF (HFpEF) (*NEJM* 2025;392:173)

Definition, epidemiology, pathophysiology

- HF iso LVEF ≥50% w/o alternate cause such as 1° myocardial, valvular or pericardial dis. if very thick walls → HCMP or infilt. CMP; if thin walls → ischemia or constriction
- ~½ of Pts w/ HF. Typically a/w HTN, diabetes, advanced age, AF, CKD, obesity.
- Pathophysiology: confluence of ventricular stiffness, ventricular–vascular uncoupling, ↓ fxn reserve, ↓ chronotropy, pulmonary vascular & endothelial dysfunction
- Precipitants of CHF: volume overload, ischemia, tachycardia/AF, HTN

Diagnosis

- Echo: impaired relaxation (eg, e′ <9 cm/s), ↑ filling pressures (eg, E/e′ ≥15), large LA
- Exercise-induced ↑ PCWP ± inadequate ↑ stroke volume, HR, CO (stress echo or CPET)

Treatment (*JACC* 2023;81:1835)

- **Diuresis**: sx control; as poorly compliant LV, small volume Δs → large filling pressure Δs
- Rx HTN, tachycardia, ischemia
- **SGLT2i:** ~20% ↓ CV death or HF hosp (*NEJM* 2021;385:1451; 2022;387:1029)
- **RASi:** nonsignif trend ↓ D/HF w/ ARB vs. pbo & w/ ARNI vs. ARB; ∴ ARNI reasonable
- **MRA**: ~18% ↓ HF hosp, but only nonsignificant ~8% reduction in CV death (*NEJM* 2014;370:1383 & 2024;391:1475; *Lancet* 2024;404:1119)
- **GLP-1RA**: if BMI ≥30 kg/m^2, improve sx & ~35% ↓ CVD or HF hosp (*Lancet* 2024;404:949; *NEJM* 2025;392:427)

CARDIOMYOPATHIES

Diseases with mechanical and/or electrical dysfunction of the myocardium

Dilated Cardiomyopathy (DCM)

Definition and epidemiology (*EHJ* 2023;44:3503)

- **LV or biventricular dilatation and global ↓ contractility** ± ↓ wall thickness in absence of ischemia/infarct or abnl loading conditions (eg, primary valvular disease or HTN). Pts w/ prior MI complicated by LV dilation and ↓ EF are often termed “ischemic CMP. ”

Etiologies (*JACC* 2021;77:2551)

- **Familial/genetic** (>35%): Pt & ≥2 1st- or 2nd-degree family members w/ unexplained DCM; >60 genes identified to date, encoding structural & nuclear proteins (eg, titin)
- **Idiopathic** (<20%): ? undx infectious, EtOH, or genetic cause; ¼ w/ e/o DCM in relative
- **Toxic:** alcohol (~20%) typ. 5 drinks/d × >5 y, but variable; cocaine; XRT (usu RCMP); anthracyclines (risk ↑ >550 mg/m^2, may manifest late), CYC, trastuzumab, TKIs
- **Infectious** (10–15%): most common = viral myocarditis; other: HIV, Chagas, Lyme

- **Infiltrative** (5%): amyloid typically RCMP (qv), but can be DCM with thickened walls; sarcoidosis (usually dilated); hemochromatosis (RCMP → end-stage dilates)
- **Peripartum** (onset 3rd trimester → 5 mo postpartum; *NEJM* 2024;390:154): ~1:2000; ↑ risk w/ multip, ↑ age, Black, 15–20% w/ mutation in DCM gene; stnd HF Rx (if preg, no RASi, spironolact., SGLT2i); ~30% recur w/ next preg → refer to cardio-OB
- **Stress-induced** (Takotsubo = apical ballooning; *JACC* 2018;72:1955): typically postmenopausal ♀; mimics MI (chest pain, ± STE & ↑ Tn; deep TWI & ↑ QT); mid/apex dyskinesis; ? Rx w/ βB, ACEI; usu. improves in wks. In-hosp morb/mort similar to ACS.
- **Tachycardia**: likelihood ∝ rate/duration; usu. resolves w/ rate/rhythm cntl
- **CTD/vasculitis** (<5%): typically assoc. w/ myopericarditis; SLE, SS, PAN, RA, EGPA
- **Arrhythmogenic right ventricular cardiomyopathy** (ACM/ARVC): fibrofatty replacement of RV → dilation (dx w/ MRI); ECG: ± RBBB, TWI V_1–V_3, ε wave; VT risk (*JACC* 2024;83:2214)
- **LV noncompaction** (*Lancet* 2015;386:813): prominent trabeculae, arrhythmias, cardioemboli
- **Metab/other:** hypothyroid, acromegaly, pheo, cirrhosis, vit B_1, selenium or carnitine defic.

Clinical manifestations

- **Heart failure:** both congestive & poor forward flow sx; signs of L- & R-sided HF **diffuse**, **laterally displaced PMI**, **S3**, ± MR or TR (annular dilat., displaced pap. muscle)
- Embolic events (~10%), supraventricular/ventricular arrhythmias, & palpitations

Diagnostic studies and workup (*Circ* 2022;145:e876; *EHJ* 2023;44:3503)

- ECG: may see PRWP, Q waves, or BBB; low voltage; AF (20%); AVB; may be normal
- Echocardiogram: LV dilatation, ↓ EF, *regional or global* LV HK ± RV HK, ± mural thrombi
- Cardiac MRI: high Se for myocarditis or infiltration; extent of scar correlated w/ mortality
- Labs: TFTs, Fe panel, HIV, SPEP, ANA; viral sero *not* recommended; others per suspicion
- Family hx (20–35% w/ familial dis.), genetic counseling & testing (*JAMA* 2009;302:2471)
- Coronary CT angiography (or invasive) to r/o CAD if risk factors, h/o angina, Qw MI
- Endomyocardial biopsy: consider if fulminant myocarditis or suspect infiltrative disease

Treatment (see “Heart Failure” for standard HF Rx)

- Possibility of reversibility of CMP may temper implantation of devices
- Prognosis differs by etiology: postpartum (best), ischemic/GCM (worst)

Myocarditis (*NEJM* 2022;387:1488; *JACC* 2025;85:391)

Etiologies

- **Infectious** (*Lancet* 2012;379:738; *JACC* 2012;59:779)
  - Viruses (parvo B19, Coxsackie, adeno, HIV, SARS-CoV-2/vaccine, etc.)
  - Bacterial, fungal, rickettsial, TB, Lyme (mild myocarditis, often with AVB)
  - Chagas: apical aneurysm ± thrombus, RBBB, megaesophagus/colon (*Lancet* 2018;391:82)
- **Autoimmune**
  - Idiopathic giant cell myocarditis (GCM): avg age 42, fulminant, AVB/VT (*Circ HF* 2013;6:15)
  - Eosinophilic (variable peripheral eos): hypersensitivity (mild HF but at risk for SCD) or acute necrotizing eosinophilic myocarditis (ANEM; STE, effusion, severe HF)
  - Collagen vasc. dis. (pericarditis > myocarditis): PM, SLE, scleroderma, PAN, RA, EGPA
- **Immune checkpoint inhibitors (ICI):** due to molecular mimicry, stop ICI if concern

Clinical manifestations

- Highly variable, ranging from incidental dx based on labs/imaging to fulminant HF w/ shock
- Can present like ACS (chest pain, ECG Δs, ↑ Tn but w/o rapid fall), ADHF, arrhythmias

Diagnostic studies and workup

- Echo: ± systolic dysfxn (typically global but can be regional); ± ↑ LV wall thickness due to edema; LV size may be small in fulminant and dilated in chronic; ± pericardial effusion
- Cardiac MRI: can show hyperemia, edema, and scar (*JACC* 2009;53:1475)
- Endomyocardial biopsy: useful in GCM & eosinophilic; ∴ consider if rapidly progressive HF, high-grade AVB or sustained VT, suspected allergic rxn or eosinophilia

Treatment

- Standard HF Rx if LV dysfxn (but do not start if e/o shock); temporary MCS as needed
- Immunosuppression: for GCM (high-dose steroids + [CsA or tacrolimus] ± AZA), collagen vascular disease, peripartum (? IVIg), ICI & eosinophilic; no proven benefit if viral

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Hypertrophic Cardiomyopathy (HCM) (Circ 2024;149:e1239)

Definition, epidemiology, pathology

- LV (usually ≥15 mm) and/or RV hypertrophy disproportionate to hemodynamic load
- Due to gene mutations affecting proteins of or related to sarcomere; prev.: ~1/200–500
- Myocardial fiber disarray with hypertrophy, which creates arrhythmogenic substrate
- Many morphologic hypertrophy variants: asymmetric septal; concentric; midcavity; apical
- Ddx LVH: HTN, AS, elite athletes (wall usu. <13 mm, symmetric & nl diastology; *Circ* 2011;123:2723), infiltrative CMP (amyloid), non-sarcomeric genetic syndromes (eg, Fabry's)

Pathophysiology

- Dynamic LV outflow tract obstruction (LVOTO) in ≥70%: narrowed tract 2° hypertrophied septum + systolic anterior motion (SAM) of ant. MV leaflet (variable) and papillary muscle displacement. Pressure gradient (∇) across LVOT worse w/ ↑ contractility (digoxin, β-agonists, exercise, PVCs), ↓ preload (eg, Valsalva maneuver) or ↓ afterload.
- Mitral regurgitation: due to SAM (mid-to-late, post.-directed regurg. jet) and/or abnl mitral leaflets & papillary muscles (pansystolic, ant.-directed regurg. jet)
- Diastolic dysfunction: ↑ chamber stiffness + impaired relaxation
- Ischemia: small vessel dis., perforating artery compression (bridging), ↓ coronary perfusion

Clinical manifestations (70% are asymptomatic at dx)

- **Dyspnea** (90%): due to ↑ LVEDP, MR, and diastolic dysfunction
- **Angina** (25%) even w/o epicardial CAD; microvasc. dysfxn (*NEJM* 2003;349:1027)
- **Arrhythmias** (AF in 20–25%; VT/VF): palpitations, syncope, sudden cardiac death

Physical exam

- Sustained PMI, S_2 paradoxically split if severe outflow obstruction, ⊕ S_4 (occ. palpable)
- **Systolic murmur:** crescendo–decrescendo; LLSB; ↑ **w/ Valsalva** & standing (↓ preload)
- ± mid-to-late or holosystolic murmur of MR at apex
- Bifid (biphasic) carotid pulse (brisk rise, decline, then 2nd rise); JVP w/ prominent *a* wave
- Contrast to AS, which has murmur that ↓ w/ Valsalva and ↓ carotid pulses

Diagnostic studies

- ECG: LVH, anterolateral TWI and inferior pseudo-Qw, ± apical giant TWI (apical variant)
- **Echo:** any LV wall segment ≥15 mm (13–14 mm if ⊕ FHx), often involving septum; ± dynamic outflow obstruction, SAM, or MR; exercise echo may provoke ↑ LVOT ∇

- MRI: hypertrophy + patchy delayed enhancement (useful for dx & prog) (*Circ* 2015;132:292)
- Cardiac cath: subaortic pressure ∇; *Brockenbrough sign* = ↓ pulse pressure post-PVC (in contrast to AS, in which pulse pressure ↑ post-PVC); spike & dome Ao pressure pattern
- Consider genotyping for family screening; pathogenic variant ID'd in <½ (*Circ* 2020;142:e558)

Treatment

- Heart failure
  - ⊖ **inotropes/chronotropes:** β-blockers, CCB (verapamil), disopyramide
    Careful w/ diuretics, b/c ↓ preload. If LVOTO, *avoid vasodilators* and digoxin.
    If sx refractory to drug Rx + *obstructive* physio. (∇ ≥30 mmHg at rest or w/ provocation):
    (a) **Cardiac myosin inhibitors**: mavacamten & aficamten (invest.) ↓ LVOTO & sx and ↑ fxnl capacity (*Lancet* 2020;396:750; *JACC HF* 2023;7:735; *NEJM* 2024;390:1849). LVEF must be ≥55% and requires monitoring as can ↓ by ~4%, greater in some.
    (b) Surgical myectomy: long-term ↓ symptoms in 90% Pts (*Circ* 2014;130:1617)
    (c) Alcohol septal ablation (*JACC* 2018;72:3095): ∇ ↓ by ~80% & 5–20% w/ residual NYHA III–IV sx; 14% req. repeat procedure. Good alt for older Pts w/ comorbidities. Complic: transient (& occ. delayed) 3° AVB w/ 10–20% req. PPM; VT due to new scar
    (d) Transcatheter myotomy: under investigation (*JACC* 2024;83:1257)
    If refractory to drug therapy and there is *nonobstructive* pathophysiology: transplant
- Acute HF: can be precip. by dehydration or tachycardia; Rx w/ fluids, βB, phenylephrine
- AF: rate control w/ βB/non-DHP CCB, maintain SR w/ DCCV, disopyramide or amio; a/c indicated regardless of CHA_2DS_2-VASc score given high stroke risk
- ICD if VT/VF. Reasonable for 1° prevention if ≥1 risk factor: ⊕ FHx SCD, unexplained syncope, LV wall ≥30 mm, LV aneurysm or EF <50%; consider if NSVT, failure of SBP to ↑ or fall from peak ≥20 mmHg w/ exercise, extensive MRI delayed enhancement. EPS *not* useful. AHA HCM Risk-SCD Score online.
- Avoid dehydration, extreme exertion. Vigorous exercise may be okay (*JAMA Card* 2023;8:595).
- 1st-degree relatives: screen w/ TTE q12–18m as teen or athlete then q5y as adult, ECG (because timing of HCMP onset variable). Genetic testing if known mutation.

Restrictive & Infiltrative CMP

Definition (*JACC* 2018;71:1130 & 1149)

- Restrictive CMP: ↓ ventricular filling due to ↓ compliance in nonhypertrophied, nondilated ventricles; nl/↓ diastolic volumes, nl or near-nl EF; must r/o pericardial disease
- Infiltrative CMP: myocardial deposition; ± ↑ wall thickness; may present as RCM or DCM

Etiologies (*JACC* 2018;71:1130 & 1149)

- **Amyloidosis** (*JAMA* 2024;331:778): age at presentation ~60 y; ♂:♀ = 3:2
  AL (eg, MM); familial (transthyretin, ATTR-m); ATTR-wt; AA (produced by liver)
  ECG: ↓ QRS amplitude (50%), pseudoinfarct pattern (Qw), AVB (10–20%), hemiblock (20%), BBB (5–20%)
  Echo: ↑ LV/RV wall thickness (*yet w/ low voltage on ECG*), granular sparkling (30%), biatrial enlargement (40%), valve thickening, small effusions
  Normal ECG voltage & septal thickness has NPV ~90%
  Cardiac MRI: distinct late gadolinium enhancement pattern (*JACC* 2008;51:1022)
- **Sarcoidosis** (*Circ* 2024;149:e1197): presents at age ~30 y; ↑ in Blacks, N. Europe, ♀
  Cardiac involvement in 25–58% of sarcoid, many not overt; cardiac w/o systemic in 10%
  ECG: AVB (75%), RBBB (20–60%), VT; PET: ↑ FDG uptake in affected area
  Echo: regional WMA (particularly basal septum) w/ thinning or mild hypertrophy or DCM
  Cardiac MRI: T2 early gad (edema); fibrosis/scar in basal septum; LGE prognostic
- **Other myocardial processes**

Hemochromatosis: often middle-aged men (espec N. European); 15% w/ cardiac sx
Diabetes; radiation (also accelerated athero, valvular disease, constrictive pericarditis)
Autoimmune (scleroderma, polymyositis–dermatomyositis)

- **Endomyocardial diseases**: carcinoid heart disease (R-sided HF w/ TR/TS, PR/PS, left-sided valves with PFO); Löffler's endocarditis (↑ eos; mural thrombi that can embolize; fibrosis); endomyocardial fibrosis (tropical climates; resembles Löffler's but w/o eos)
- **Storage diseases**: Fabry (glycosphingolipids); Gaucher (glucocerebrosidase)

Pathophysiology & clinical manifestations (*JACC* 2018;71:1130 & 1149)

- ↓ myocardial compliance → ↑ filling pressures; ↓ ventricular cavity size → ↓ SV and ↓ CO
- Both **L & R HF** w/ periph. edema ± ascites & pulm edema; DOE & poor exercise tolerance
- **Diuretic "refractoriness"** w/ AKI; thromboemboli
- Poorly tolerated atrial/ventricular tachyarrhythmias; infiltrative → VT → syncope/SCD

Physical exam

- ↑ JVP, ± Kussmaul's sign (JVP not ↓ w/ inspir., classically seen in *constrict. pericarditis*)
- Cardiac: ± S_3 and S_4, ± murmurs of MR and TR
- Peripheral & pulmonary edema; congestive hepatomegaly ± ascites & jaundice

Diagnostic studies (*JACC* 2022;79:372)

- ECG: low voltage, pseudoinfarction pattern (Qw), ± arrhythmias
- Echo: ± symmetric wall thickening, biatrial enlarge., ± mural thrombi, ± cavity oblit. w/ diast dysfxn: ↑ early diast (E) and ↓ late atrial (A) filling, ↑ E/A ratio (restrictive pattern); ↓ mitral annular velocity (e′) on tissue Doppler, ↑ E/e′ ratio; ↑ TR velocity
- Labs: NT-proBNP, serum & urine immunofixation electrophoresis (IFE), serum free light chains (SFLC), Fe ± HFE mutation
- Cardiac MRI/PET: may reveal inflammation or evidence of infiltration (but nonspecific)
- Amyloid (qv) eval: ✓ for plasma cell dyscrasia (IFE & SFLC). If ⊕ → fat pad bx. If ⊖ → PYP SPECT for TTR eval → if ⊕ → TTR gene sequencing.
- Endomyocardial biopsy if suspect amyloid (Se ~100%) & noninvasive tests non-dx. Se low for sarcoidosis b/c patchy disease infiltrative process.
- Cardiac catheterization (see "Pericardial Disease" for restrictive vs. constrictive processes)
  Atria: **M's** or **W's** (prominent *x* and *y* descents)
  Ventricles: **dip & plateau** (rapid ↓ pressure at onset of diastole, rapid ↑ to early plateau)
  Concordance of LV–RV pressure peaks w/ respiration (vs. discordance in constriction)

Treatment (*JACC* 2022;79:372; in addition to Rx'ing underlying disease)

- Gentle diuresis (goal ⊖ ≤1 L/d). May not tolerate CCB or other vasodilators.
- Control HR (but can ↓ CO); maintain SR (helps filling). Digoxin ↑ arrhythmias in amyloid.
- Anticoagulation (if AF regardless of CHA_2DS_2-VASc; ? if ↓↓ CO); ? transplant if refractory
- AL amyloid: Rx targeted at plasma cell dyscrasia
- ATTR amyloid: TTR stabilizers (eg, tafamidis & acoramidis) improve sx & fxnal capacity and ↓ death & CV hosp (*NEJM* 2018;379:1007 & 2024;390:132); TTR siRNA (eg, patisiran & vutrisiran) preserve fxnal capacity and ↓ death & CV hosp (*NEJM* 2023;389:1553 & 2025;392:33)
- Sarcoid: consider steroids/immunomodulators if FDG-PET ⊕ for inflammation + AVB, VT or LV dysfxn; ↑ risk for VT; unique indications for ICD placement (*Circ* 2018;138:e272)

VALVULAR HEART DISEASE

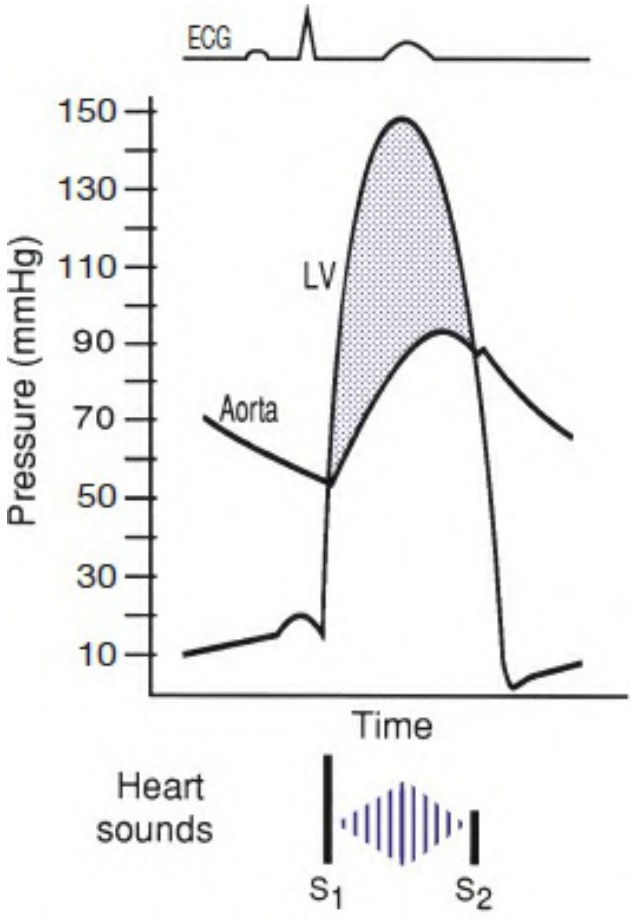
Aortic Stenosis (AS) (*JAMA* 2024;332:2014)

Etiology

- **Calcific:** predominant cause in Pts >70 y; risk factors: HTN, ↑ LDL-C, ↑ Lp(a), ESRD
- **Congenital** (ie, bicuspid AoV w/ premature calcification): cause in 50% of Pts <70 y
- **Rheumatic heart disease** (AS usually accompanied by AR and MV disease)
- AS mimickers: subvalvular (HCMP, subaortic membrane) or supravalvular stenosis

Clinical manifestations (usually indicates AVA **<1** cm^2 or concomitant CAD)

- **Angina:** ↑ O_2 demand (hypertrophy) + ↓ O_2 supply (↓ cor perfusion pressure) ± CAD
- **Syncope** (*exertional*): peripheral vasodil. w/ fixed CO → ↓ MAP → ↓ cerebral perfusion
- **Heart failure:** outflow obstruct + diastolic dysfxn → pulm. edema, esp. if ↑ HR/AF (↓ LV fill.)
- Acquired vWF disease (~20% of sev. AS): destruction of vWF; GI angiodysplasia
- Natural hx: usually slowly progressive (AVA ↓ ~0.15 cm^2/y, but varies; *Circ* 1997;95:2262), until sx develop; mean survival based on sx: angina = 5 y; syncope = 3 y; CHF = 2 y



Pathophys Heart Disease, 7th ed, 2021, for this et al.

Physical exam

- **Midsystolic crescendo–decrescendo** murmur at **RUSB**, harsh, high-pitched, radiates to carotids, apex (holosystolic = Gallavardin effect), ↑ w/ passive leg raise, ↓ w/ standing & Valsalva. Dynamic outflow obstruction (HCM) is the reverse.

- Ejection click after S_1 sometimes heard with *bicuspid* AoV
- Signs of severity: *late-peaking* murmur, paradoxically split S_2 or inaudible A_2, small and delayed carotid pulse ("*pulsus parvus et tardus*"), LV heave, ⊕ S_4 (occasionally palpable)

Diagnostic studies

- ECG: may see LVH, LAE, LBBB, AF (in late disease)
- CXR: cardiomegaly, AoV calcification, post-stenotic dilation of ascending Ao, pulmonary congestion
- **Echo:** valve morph., jet velocity → estimate pressure gradient (∇) & calculate AVA, dimensionless index (DI); LVEF
- **Cardiac cath:** usually to *r/o CAD* (in ~½ of calcific AS); for hemodyn. if disparity between exam & echo: ✓ pressure gradient (∇) across AoV, calc AVA (underestim. if mod/sev AR)
- **Low-flow, low-gradient (LFLG) severe AS:** AVA ≤1, but mean ∇ <40. "Classical" due to LVEF <50% due to afterload mismatch from AS or myocardial process. "Paradoxical" iso nl LVEF but small LV (eg, HTN or amyloid).
- **Dobutamine challenge** (echo or cath) can be used in potential LFLG to differentiate *afterload mismatch* (20% ↑ SV & ∇, no Δ AVA; implies good contractile reserve) vs. *pseudostenosis* (20% ↑ SV, no Δ in ∇, ↑ AVA; implies low AVA *artefact* of LV dysfxn)
- **Cardiac CT:** AoV calcium score can be used in LFLG to assess AS severity

Classification of Aortic Stenosis (*Circ* 2021;143:e72)

Stage	Sx	Severity	Max Jet Vel ($^m/_s$)	Mean ∇ (mmHg)	AVA (cm^2)[a]	LVEF	DI
n/a	N	Normal	1	0	3–4	nl	n/a
A	N	At risk	<2	<10	3–4	nl	n/a
B	N	Mild	2–2.9	<20	>1.5	nl	>0.5
		Moderate	3–3.9	20–39	1–1.5	nl	0.25–0.5
C1	N	Severe	≥4	≥40	≤1.0	nl	<0.25
		Very severe	≥5	≥60	≤0.8	nl	
C2		Severe + ↓ EF	≥4	≥40	≤1.0	↓	
D1	Y	Severe	≥4	≥40	≤1.0	nl	<0.25
D2		Severe + low flow/∇ + ↓ EF[b]	<4	<40	≤1.0	↓	
D3		Severe + low flow/∇ + nl EF[c]	<4	<40	≤1.0	nl	

[a]AVA indexed to BSA <0.6 cm^2/m^2 also severe (use for smaller Pts); [b]DSE → max jet vel ≥4 & AVA ≤1.0; [c]Small LV w/ ↓ stroke vol (LVSVi <35 mL/m^2), severe LVH with marked diastolic dysfunction, consider cardiac amyloid

Valve replacement (*Circ* 2021;143:e72)

- Based on *symptoms:* once they develop → AVR needed
- *Indicated in:* **sx severe** (stage D1; D2; D3 if AS felt to be cause of sx); **asx severe** + **EF <50%** (stage C2); or severe (stage C1) *and* undergoing other cardiac surgery
- *Reasonable if:* **asx severe** (C1) *but* either ↓ **BP or sx w/ exercise** (can *carefully* exercise asx AS to uncover sx; do *not* exercise sx AS), **very severe,** ↑ BNP, rapid progression

- Asx severe AS: ↓ hosp, ? death (if nearly very severe) (*EHJ* 2024;45:4526; *NEJM* 2025;392:217)

Valve selection

- **Mechanical** (more durable, but done surgically and requires lifelong a/c) vs. **bioprosthetic**
- Pt <50 y: SAVR. Pt 50–65 y: either. Pt >65 y or ⌀ a/c: bioprosthetic (by TAVI or SAVR)

TAVI (transcatheter AoV implantation) (*JAMA* 2021;325:2480; *Circ* 2021;143:e72)

- Balloon-expandable or self-expanding. Usually transfemoral access (best outcomes).
- TAVI noninferior to SAVR in terms of risk of death or disabling stroke for Pts of any surgical risk (*NEJM* 2014;370:1790; 2020;382:799; *NEJM* 2023;389:1949 & 2024;390:1572; *JACC* 2023;82:2163)
- In *nonoperative Pts* (ie, vs. med Rx): ↓ mortality but still ~72% at 5 y (*Lancet* 2015;385:2485)
- Complications: CHB ~15% at 30 d, more common if preexisting RBBB (*JACC* 2020;76:2391); annular rupture or coronary occlusion (both rare); stroke; local vascular; paravalvular leaks; "suicide" left ventricle due to dynamic intraventricular pressure ∇ (Rx like HCM)
- Postprocedural antithrombotic Rx: ASA 75–100 mg/d (*NEJM* 2020;383:1447). In Pts *with indication for OAC*: OAC alone superior to OAC + $P2Y_{12}$ (*NEJM* 2020;382:1696); apixaban & edoxaban appear comparable to warfarin (*NEJM* 2021;385:2150; *EHJ* 2022;42:2783).

Other therapy

- If not AVR candidate or to temporize: careful diuresis prn (preload-dependent physiology)
- Control HTN. Maintain SR; digoxin if ↓ EF & HF or if AF. *Avoid* venodilators (nitrates) & ⊖ inotropes (βB/CCB) if severe AS. Avoid vigorous physical exertion once AS mod–severe.
- If cardiogenic shock: inotropes; IABP (especially if CAD) vs. Impella
- Afterload reduction (eg, SNP) w/ PAC if HF w/ sev. AS, ↑↑ SVR & BP nl (*Circ* 2013;128:1349)

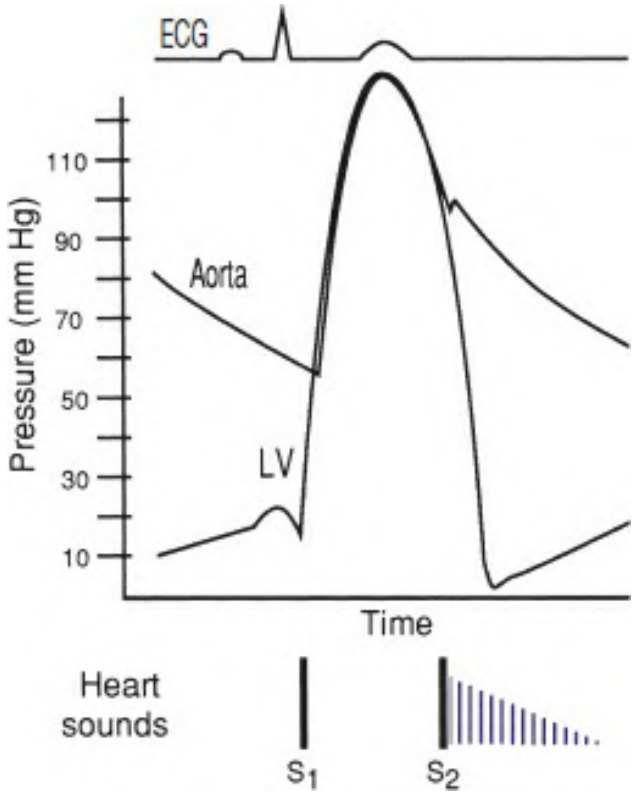
Aortic Regurgitation (AR)

Etiology (*Circ* 2006;114:422)

- **Valve disease** (~45%): **rheumatic** (usually mixed AS/AR + MV disease); **bicuspid AoV** (natural hx: 1/3 → normal, 1/3 → AS, E 1/6 → AR, 1/6 → endocarditis → AR); **infective endocarditis;** valvulitis (RA, SLE, certain anorectics & serotonergics, XRT)
- **Root disease** (~55%): **HTN**, aortic aneurysm/dissection, annuloaortic ectasia (ie, Marfan), **aortic inflammation** (GCA, Takayasu's, ankylosing spond., reactive arthritis, syphilis)

Clinical manifestations

- **Acute**: sudden ↓ forward SV and ↑ LVEDP (noncompliant ventricle) → pulmonary edema ± hypotension and cardiogenic shock
- **Chronic**: clinically silent while LV dilates (to ↑ compliance to keep LVEDP low) more than it hypertrophies → chronic volume overload → LV decompensation → CHF
- **Natural hx**: *variable* progression (unlike AS, can be fast or slow); once decompensation begins, prognosis poor w/o AVR (mortality ~10%/y)



Physical exam

- **Early diastolic decrescendo murmur at LSB** (RSB if dilated Ao root); ↑ w/ sitting forward, expir, handgrip; severity of AR ∝ duration of murmur (except in acute and severe late); *Austin Flint murmur:* mid-to-late diastolic rumble at apex (AR jet interfering w/ mitral inflow)
- **Wide pulse pressure** + **low DBP** due to ↑ stroke volume; hyperdynamic pulse; pulse pressure narrows in late AR with ↓ LV fxn; bisferiens (twice-beating) arterial pulse
- PMI diffuse and laterally displaced; soft S_1 (early closure of MV); ± S_3 (≠ ↓ EF but rather just volume overload in AR)

Classic Eponymous Signs in Chronic AR (*South Med J* 1981;74:459)	
Sign	**Description**
Corrigan's pulse	"water hammer" pulse (ie, rapid rise/fall or distention/collapse)
Hill's sign	(popliteal SBP – brachial SBP) >60 mmHg
Duroziez's sign	to-and-fro murmur heard over femoral artery w/ light compression
Pistol shot sounds	pistol shot sound heard over femoral artery
Traube's sound	double sound heard over femoral artery when compressed distally
de Musset's sign	head-bobbing with each heartbeat (low Se)
Müller's sign	systolic pulsations of the uvula
Quincke's pulses	subungual capillary pulsations (low Sp)

Diagnostic studies

- ECG: can see LVH, LAD, abnl repol; CXR: cardiomegaly ± ascending Ao dilatation

- **Echo:** severity of AR (severe = regurg jet width ≥65% LVOT, regurg fraction ≥50%, effective regurg orifice ≥0.3 cm^2, holodiastolic flow reversal in prox abd Ao; moderate = jet width 25–64%, regurg fraction 30–49%, regurg orifice 0.1–0.29 cm^2); LV size & fxn

Treatment (*Lancet* 2016;387:1312; *Circ* 2021;143:e72)

- Acute decompensation (consider endocarditis as possible acute precipitant): *surgery* usually urgently needed for acute severe AR, which is poorly tolerated by LV IV afterload reduction (eg, nitroprusside) & inotropic support (dobutamine) ± chronotropic support (↑ HR → ↓ diastole → ↓ time for regurg.) pure vasoconstrictors, βB & IABP contraindicated
- Chronic AR: management decisions based on *LV size and fxn* (and before sx occur); low diastolic BP and high resting HR associated with mortality (*JACC* 2020;75:29)
- **Surgery** (AVR, replacement or repair if possible):
  Severe and **sx** (if equivocal, consider stress test)
  Asx *and* either **EF ≤55%**, **LV dilation** [LVESD >50 mm or LVESDi (indexed to BSA) ≥ 25 mm/m^2 (*JACC* 2019;73:1741)], or **undergoing cardiac surg**
- TAVI not approved for pure AR, under investigation (*Lancet* 2024;403:1451)
- Medical therapy: **vasodilators** (nifedipine, ACEI/ARB, hydralazine) if severe AR w/ sx or LV dysfxn & not operative candidate or to improve hemodynamics before AVR

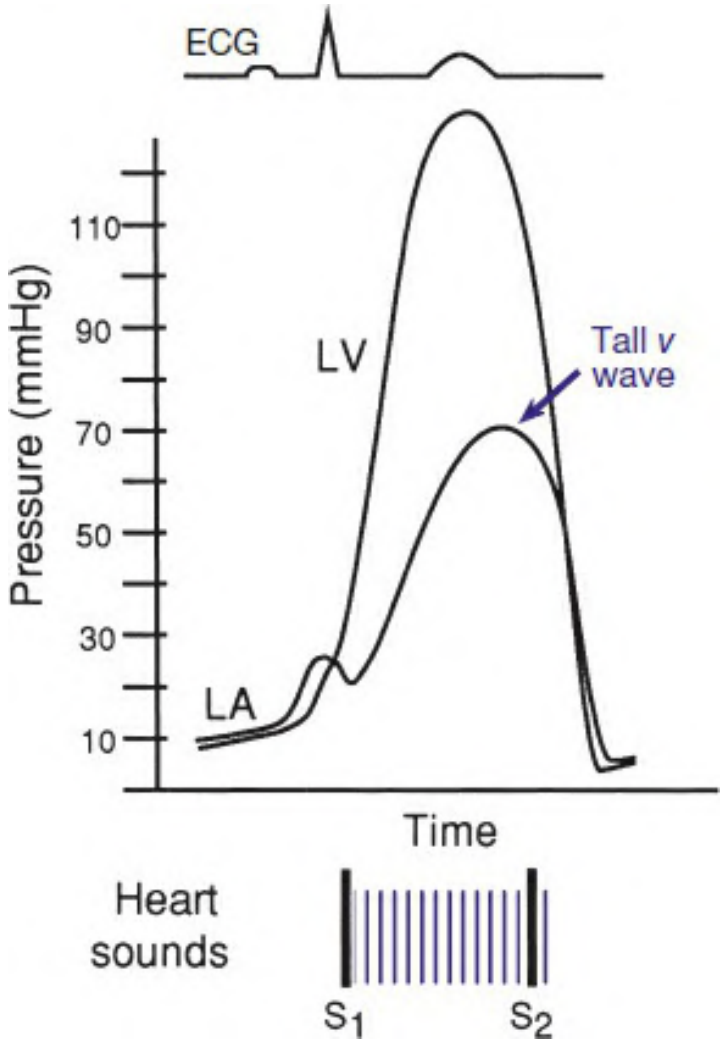
Mitral Regurgitation (MR)

Etiology (*NEJM* 2010;363:156 & 2020;383:1458)

- **Primary** (~2/3; degeneration of valve apparatus)
  Leaflet abnl: myxomatous (MVP), endocarditis, calcific, RHD, valvulitis (collagen vascular disease), congenital (eg, cleft), anorectic drugs (phen-fen), XRT
  Chordae tendineae rupture: myxomatous, endocarditis, spontaneous, trauma
  Papillary muscle dysfxn b/c of ischemia or *rupture* during MI [usu. posteromedial papillary m. (supplied predominantly by PDA) vs. anterolateral (suppl. by diags & OMs)]
- **Secondary** (~1/3; functional): inferoapical papillary muscle displacement due to ischemic LV remodeling or DCM; HCM (*JACC* 2015;65:1231); atrial remodeling (lack of coaptation)
- In 1° MR, leaflet prolapsing into LA; jet directed to opposite side of prolapsing leaflet
- In 2° MR, leaflet tethering, jet directed centrally or to same side as tethered leaflet

Clinical manifestations

- Acute: **pulmonary edema**, hypoxia, hypotension, cardiogenic shock (*NEJM* 2004;351:1627)
- Chronic: typically asx for yrs, then as LV fails → progressive DOE, fatigue, AF, PHT
- Prognosis. In 1°: 5-yr survival w/ meds is ~70% if asx, ~15% if NYHA Class III–IV (*NEJM* 1996;335:1417). In 2°: 2-yr survival ~20–30% (*JACC* 2015;65:1231).



Physical exam

- **High-pitched, blowing, holosystolic murmur at apex;** radiates to axilla; ± thrill; ↑ w/ handgrip (Se 68%, Sp 92%), ↓ w/ Valsalva (Se 93%)
  - ant. jets heard at sternum & base of heart
  - post. jets heard at axilla, infrascap, & spine
- ± diastolic rumble b/c ↑ flow across valve
- Lat. displ. hyperdynamic PMI, obscured S_1, widely split S_2 (A_2 early b/c ↓ LV afterload, P_2 late if PHT); ± S_3
- Carotid upstroke brisk (vs. diminished and delayed in AS)

Diagnostic studies (*Circ* 2021;143:e72)

- ECG: may see LAE, LVH, ± atrial fibrillation
- CXR: dilated LA, dilated LV, ± pulmonary congestion
- **Echo:** MV anatomy (ie, etiol); MR severity: jet area, jet width at origin (vena contracta) or effective regurgitant orifice (ERO; predicts survival); LV fxn (EF should be *supranormal*, ∴ EF <60% w/ sev. MR = LV dysfxn). W/ exercise if suspect exertional ↑ in MR severity.
- TEE or cardiac MR if TTE not sufficiently informative or being considered for intervention
- Cardiac cath: prominent PCWP *c-v* waves (not spec. for MR), LVgram for MR severity & EF

Grading of Primary Mitral Regurgitation						
Severity	Regurg. Fraction	Jet Area (% of LA)	Vena Contracta (cm)	ERO (cm^2)	Pulm vein systolic flow[a]	Angio[b]
Mild	<30%	<20	<0.3	<0.2	nl	1+
Moderate	30–49%	20–40	0.3–0.69	0.2–0.39	nl/blunting	2+
Severe	≥50%	>40	≥0.70	≥0.40[c]	reversal	3/4+

[a]Influenced by LV function, etc. [b]1+ = LA clears w/ each beat; 2+ = LA does not clear, faintly opac. after several beats; 3+ = LA & LV opac. equal. [c]For 2° MR, ERO ≥0.20 severe as underestimated & likely LV dysfxn.

Treatment (*Circ* 2021;143:e72)

- **Acute severe MR:** consider ischemia & endocarditis as precipitants; IV afterload reduction (nitroprusside), relieve congestion (diuresis & NTG), ± inotropes (dobuta), IABP, avoid vasoconstrictors; *surgery* usually needed b/c prognosis poor w/o (*JAMA* 2013;310:609)
- **Chronic severe *primary* MR: surgery** (repair [preferred if feasible] vs. replacement) if **sx; asx & either EF ≤60% or LVESD ≥40 mm**; and reasonable if low surgical risk + high prob successful repair; consider transcatheter repair if not surg candidate
- For primary MR, surgery superior to percutaneous repair (*NEJM* 2011;364:1395)
- If undergoing surgery & AF, MAZE ↓ AF recurrence, Ø Δ stroke (*NEJM* 2015;372:1399); surgical LAA occlusion ↓ risk of stroke; nb, Pts remained on anticoag (*NEJM* 2021;384:2081)
- **Chronic sx severe *secondary* MR:** if on optimal GDMT, EF 20–50%, LVESD ≤70 mm, & PASP ≤70 mmHg**, transcatheter edge-to-edge repair** (mTEER) → 25–30% ↓ death or HF hosp (*NEJM* 2018;379:2297 & 2307; 2024;391:1799; *JACC* 2024;84:2364); consider MV surgery if EF ≥50% or EF ≤50% but not meeting criteria for repair
- Transcatheter replacement (TMVR) remains under study (*JACC Intv* 2021;14:489)
- If sx & EF <60% but not operative candidate: Rx (βB, ACE/ARB ± MRA); ↓ preload w/ diuretics, NTG (espec. if ischemic MR) for sx relief ± ↓ ERO; maintain SR
- Asymptomatic: Ø proven benefit of medical therapy; βB ↑ LV fxn (*JACC* 2012;60:833)

Mitral Valve Prolapse (MVP)

Definition and etiology

- Billowing of MV leaflet ≥2 mm above mitral annulus in parasternal long axis echo view
- Primary: sporadic or familial myxomatous proliferation of spongiosa of MV apparatus
- Secondary: trauma, endocarditis, congenital, CTD (eg, Marfan's, OI, Ehlers–Danlos)

Clinical manifestations (usually asymptomatic)

- MR, endocarditis, emboli, arrhythmias (rarely SCD from VT from papillary muscle)
- High-pitched, midsystolic click (earlier w/ ↓ preload) ± mid-to-late systolic murmur
- No Rx *per se* [endocarditis Ppx not rec. (*Circ* 2007;116:1736)]; Rx MR as above

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Mitral Stenosis (MS)

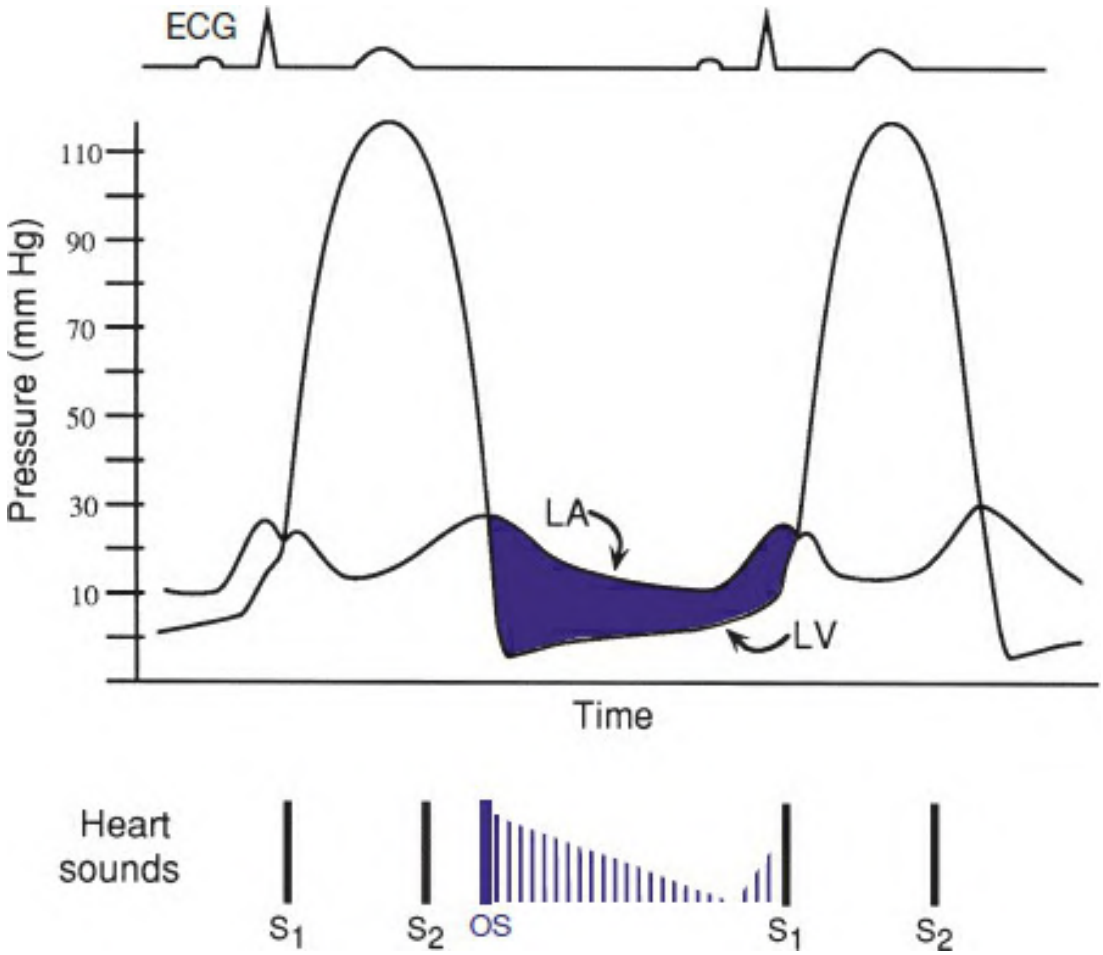
Etiology (*Lancet* 2012;379:953)

- **Rheumatic heart disease** (RHD): *fusion of commissures* → "fish-mouth" valve from autoimmune rxn to β strep infxn; seen largely in developing world (*Circ* 2020;142:e337)
- **Mitral annular calcification:** encroachment upon leaflets → fxnal MS; espec in ESRD
- Post-repair, congenital, infectious endocarditis w/ large lesion, myxoma near MV, thrombus

- Valvulitis (eg, SLE, amyloid, carcinoid) or infiltration (eg, mucopolysaccharidoses)

Clinical manifestations (*Lancet* 2009;374:1271)

- **Dyspnea and pulmonary edema** (if due to RHD, sx usually begin in 30's) precipitants: exercise, fever, anemia, volume overload (incl. pregnancy), tachycardia, AF
- **Atrial fibrillation:** onset often precipitates heart failure in Pts w/ MS
- **Embolic events:** commonly cerebral, espec in AF or endocarditis
- Pulmonary: hemoptysis, frequent bronchitis (due to congestion), PHT, RV failure
- Ortner's syndrome: hoarseness from LA compression of recurrent laryngeal nerve



Physical exam

- **Low-pitched mid-diastolic rumble at apex** w/ presystolic accentuation (if not in AF); best heard in L lat decubitus position during expiration, ↑ w/ exercise; severity proportional to *duration* (not intensity) of murmur; loud S_1
- **Opening snap** (high-pitched early diastolic sound at apex) from fused leaflet tips; MVA proportional to S_2–OS interval (tighter valve → ↑ LA pressure → shorter interval)
- Loud S_1 (unless MV calcified and immobile)

Diagnostic studies

- ECG: **LAE** ("P mitrale"), ± AF, ± RVH
- CXR: **dilated LA** (flat L heart border, R double density, displaced L mainstem bronchus)

- **Echo:** estimate pressure gradient (∇), RVSP, valve area, valve echo score (0–16, based on leaflet mobility & thick, subvalvular thick., Ca^{++}); exer. TTE (to assess Δ RVSP and ∇) if sx & severity of MS at rest discrepant; TEE to assess for LA thrombus before PMBC
- **Cardiac cath:** ∇, calculated MVA; LA tall *a* wave & blunted *y* descent; ↑ PA pressures

Stages of Mitral Stenosis				
Stage	**Mean ∇ (mmHg)**	**Pressure ½ Time**	**MVA (cm^2)**	**PA sys (mmHg)**
Normal	0	n/a	4–6	<25
Progressive	<5	<150	>1.5	≤50
Severe ± sx	>5	≥150	≤1.5	>50

Treatment (*Lancet* 2016;387:1324; *Circ* 2021;143:e72)

- Medical: Na restriction, cautious diuresis, βB, AF control, sx-limited physical stress
- Antibiotic Ppx recommended if h/o RHD w/ valvular disease for 10 y or until age 40
- Anticoag w/ warfarin (not DOAC; *NEJM* 2022;387:978) if: AF; prior embolism; LA clot
- Mechanical intervention indicated if **sx severe MS**; reasonable if asx severe MS but PASP >50 mmHg and morphology favorable for PMBC; consider PMBC if nonsevere MS but exertional sx and hemodyn signif w/ exercise, or if asx severe MS and new-onset AF
- **Percutaneous mitral balloon commissurotomy** (PMBC): preferred Rx if RHD; ≈ MVR *if* Wilkins score <8, Ø if mod–severe MR or LA clot
- Surgical (MV repair if possible, o/w replacement) if PMBC contraindicated
- Calcific MS: surgical MVR if severe & highly sx; use of transcatheter aortic prosthesis experimental and w/ high rate of complications (*Circ CVI* 2020;13:e008425)
- Pregnancy: if NYHA class III/IV → PMBC, o/w medical Rx w/ low-dose diuretic & βB

Tricuspid Regurgitation (*Circ* 2021;143:e72 & 2024;149:e1223)

- Fxnl etiol (80%): RV or RA dilation, pHTN (may be 2° to L-sided dis.), large L → R shunts
- 1° etiol: myxomatous, IE, **pacemaker leads**, RHD, CTD, XRT, Ebstein's, carcinoid, tumors
- Holosystolic murmur, 3rd/4th ICS, ↑ w/ insp (Carvallo's sign); S_3; prominent *cv* wave in JVP
- Echo: mechanism, severity, annular dilation, RV size & fxn, RVSP, left-sided disease
- Medical treatment: diuretics, rhythm control, GDMT if indication
- Consider repair/replacement in severe TR (eg, ERO ≥0.40 cm^2) undergoing L-sided surgery, R HF, or ? prog. RV dysfxn; TTVR (*JACC* 2025;85:265) & tTEER improve TR, QoL & fxnal status, ↓ hosp for HF (*NEJM* 2023;388:1833 & 2025;392:115; *JAMA* 2025;333:124; *Circ* 2025;epub)

Prosthetic Heart Valves

Mechanical

- Bileaflet (eg, St. Jude Medical); tilting disk; caged ball (no longer implanted)
- Very durable (20–30 y), but thrombogenic & ∴ require lifelong anticoagulation; consider if age <50 y or if anticoagulation already indicated

Bioprosthetic

- Bovine pericardial or porcine heterograft (eg, Carpentier-Edwards), homograft, TAVI
- Less durable, but min. thrombogenic; consider if >~65 y, lifespan <20 y, or Ø anticoag
- If 50–69 y, 2× reop but ½ bleeding or stroke vs. mech (*JAMA* 2014;312:1323 & 2015;313:1435)

Physical exam: crisp sounds ± soft murmur during forward flow (normal to have small ∇)

Anticoagulation & antiplatelet therapy (*Circ* 2021;143:e72)

- **Mechanical:** warfarin (***not DOAC***), INR 2.5–3.5 (INR 2–3 if low-risk mech AVR w/ none of following: prior thromboembolism, AF, EF <30–35%, hypercoagulable)
  If thrombosis, ↑ intensity (eg, INR 2–3 → 2.5–3.5; 2.5–3.5 → 3.5–4.5; or + ASA if not on)
- **Bioprosthetic:**
  Surgical: ASA (75–100 mg/d) or warfarin INR 2–3 ×3–6 mo, then ASA (75–100 mg/d). DOAC reasonable alternative to warfarin if indication for anticoag (*NEJM* 2020;383:2117).
  TAVI: ASA 75–100 mg/d. If need OAC, then no antiplt (vide supra).

Periprocedural "Bridging" of Anticoagulation in Pts with Mechanical Valve(s)	
AVR w/o risk factors	d/c warfarin 2–4 d before surg; restart 12–24 h after surg
MVR or AVR w/ risk factors	Pre-op: d/c warfarin 3–4 d before, start UFH (or LMWH) when INR <2 4–6 h pre-op: d/c UFH; post-op: restart UFH & warfarin ASAP

JACC 2017;70:253. Procedures include noncardiac surgery, invasive procedures, and major dental work.

Correction of overanticoagulation: weigh risks (bleeding vs. thrombosis)

- Not bleeding: if INR 5–10, withhold warfarin
- Bleeding: PCC (or FFP); reversal agent for DOACs; ± low-dose (1 mg) vit K IV if on VKA

Endocarditis prophylaxis: for all prosthetic valves (see "Endocarditis")

Complications

- Structural failure (r/o endocarditis); mech. valves: rare except Bjork–Shiley; bioprosth: up to 30% rate w/in 10–15 y, mitral > aortic; consider TAVR (*JACC* 2017;69:2253)
- Paravalvular leak (r/o endocarditis); small *central* jet of regurg is normal in mech. valves
- Obstruction from thrombosis or pannus: ✓ TTE, TEE, CTA, or fluoro significantly symptomatic
  pannus ingrowth: remove w/ surgery
  thrombosis: surgery if sx or large L-sided mech valve obstruction; UFH ± low-dose lytic if small, not surgical candidate, or R-sided; OAC for sx bioprosthetic thrombosis
- Infective endocarditis ± valvular abscess and conduction system dis. (see "Endocarditis")
- Embolization (r/o endocarditis); risk highest 1st 90 d, ~1%/y w/ warfarin (vs. 2% w/ ASA, or 4% w/o meds); mech MVR 2× risk of embolic events vs. mech AVR
- Bleeding (from anticoag), hemolysis (espec w/ caged ball valves or paravalvular leak)

PERICARDIAL DISEASE

Anatomy

- 2-layered (parietal & visceral) tissue sac surrounding heart & proximal great vessels

Disease states

- Inflammation (w/ or w/o fluid accumulation) → pericarditis
- Fluid accumulation → effusion ± tamponade
- Decrease in compliance (sequela of inflammation) → constrictive pericarditis
- Tamponade and constriction characterized by increased ventricular interdependence

Etiologies of Acute Pericarditis (*JACC* 2020;75:76)	
Idiopathic (~90%)	Most presumed to be undiagnosed viral etiologies
Infectious (<5% can be confirmed infectious)	Viral: Coxsackie, Parvovirus B19, echo, adeno, EBV, VZV, HIV, influenza, SARS-CoV-2 Bacterial (from endocarditis, pneumonia, or s/p cardiac surgery): *S. pneumo, N. meningitidis, S. aureus, Borrelia* (Lyme); TB Fungi: *Histo, Coccidio, Candida*; Parasite: *Entamoeba, Echino*
Neoplastic (<10%)	*Common:* metastatic (lung, breast, lymphoma, leukemia, RCC) *Rare:* primary cardiac & serosal tumors (mesothelioma)
Autoimmune	Connective tissue diseases: SLE, RA, scleroderma, Sjögren's Vasculitides: PAN, ANCA ⊕ (EGPA, GPA) Drug-induced: procainamide, hydralazine, inh, CsA
Uremia	~5–13% of Pts prior to HD; ~20% occurrence in chronic HD Pts
Cardiovascular	STEMI, late post-MI (Dressler's syndrome), but rare in modern era; prox AoD; chest trauma/postpericardiotomy; PCI or EP complication
Radiation	>40 Gy to mediastinum; acute or delayed; may be transudative
Effusion w/o pericarditis	HF (particularly R-sided as pericardial fluid drains into RA), cirrhosis, nephrotic syndrome, hypothyroidism, amyloidosis. Transudative.

Clinical manifestations (*NEJM* 2014;371:2410; *JACC* 2020;75:76)

- **Pericarditis:** retrosternal CP, pleuritic, positional (often ↓ by sitting forward), → trapezius; may be *absent* in TB, neoplastic, XRT, or uremic; ± fever; ± s/s of systemic etiologies
- **Effusion:** present in 50–65% of Pts w/ pericarditis; ranges from asx to tamponade
- **Definitions:** acute (<4–6 wks), incessant (persistent sx >4–6 wks), recurrent (after a symptom-free interval of 4–6 wks), chronic (lasting >3 mos)

Physical exam

- **Pericarditis:** multiphasic **friction rub** best heard at LLSB w/ diaphragm of stethoscope. Notoriously variable and evanescent leathery sound w/ up to 3 components: atrial contraction, ventricular contraction, ventricular relaxation (*NEJM* 2012;367:e20).
- **Effusion:** distant heart sounds, dullness over left posterior lung field due to compressive atelectasis from pericardial effusion (Ewart's sign)

Diagnostic studies (*JACC* 2020;75:76; *JAMA* 2024;332:1090)

- Need ≥2 of the following: chest pain (as noted above), friction rub, ECG findings, effusion
- **ECG:** may show diffuse STE (*concave up*) & PR depression (except in aVR: ST ↓ & PR ↑), TWI; classically and in contrast to STEMI, TWI do not occur until STs normalize
  - Stages: (I) STE & PR ↓; (II) ST & PR normalize; (III) diffuse TWI; (IV) Tw normalize
  - ECG may show evidence of large effusion w/ low voltage & electrical alternans (beat-to- beat Δ in QRS amplitude and/or axis due to swinging heart)
- CXR: if lg effusion (>250 mL) → ↑ cardiac silhouette w/ "water bottle" heart & epicardial halo
- **Echocardiogram:** presence, size, & location of *effusion*; presence of *tamponade physiology*; pericarditis itself w/o spec. abnl (∴ echo can be nl), although can see pericardial stranding (fibrin or tumor); can also detect LV/RV dysfxn (myocarditis?)
- CT: effusion (often larger by CT than by echo) ± calcif.; pericard. enhancement w/ contrast
- **MRI:** may reveal pericardial thickening/inflammation, as well as myocardial involvement

- ⊕ cTn in ~30%, indicative of concomitant myocarditis (*JACC* 2003;42:2144). Inflammatory biomarkers (ESR, CRP) elevated in 80% of presentations; CRP predicts recurrence.

Workup for effusion

- r/o infxn: usually apparent from Hx & CXR; ? value of ✓ acute and convalescent serologies
- r/o noninfectious etiologies: BUN, Cr, ANA, RF, HIV, screen for common malignancies
- Pericardiocentesis if suspect infxn or malignancy or large effusion (>2 cm) or recurrent
  - ✓ cell counts, TP, LDH, glc, Gram stain & Cx, AFB, cytology
  - ADA, PCR for MTb, and specific tumor markers as indicated by clinical suspicion
  - "exudate": TP >3 g/dL, TP_{eff}/TP_{serum} >0.5, LDH_{eff}/LDH_{serum} >0.6, or glc <60 mg/dL; high Se (~90%) but *very low* Sp (~20%); overall low utility (*Chest* 1997;111:1213)
- Pericardial bx if suspicion for malignancy or TB; perform during every surgical drainage

Treatment of pericarditis (*JACC* 2020;75:76; *JAMA* 2024;332:1090)

- High-dose **NSAID** (eg, ibuprofen 600–800 mg tid) or ASA (eg, 650–1000 mg tid) × 7–14 d then taper over wks; ASA preferred over NSAID in acute MI; consider PPI to ↓ risk of GIB
- **Add colchicine** 0.5 mg bid (qd if ≤70 kg) × 3 mo; 50% ↓ risk of refractory or recurrent pericarditis (*NEJM* 2013;369:1522). Amio, dilt, verap, & atorva ↓ P-gp and/or CYP3A4 & ↑ risk of colchicine tox espec if renal/hepatic impairment.
- Avoid steroids except for systemic autoimmune disorder, uremia, preg., NSAIDs contra-indicated. Appear to ↑ rate of pericarditis recurrence; risk lower w/ low-dose wt-based (ie, prednisone 0.2–0.5 mg/kg) with slow taper (*Circ* 2008;118:667 & 2011;123:1092).
- Avoid anticoagulants (although no convincing data that ↑ risk of hemorrhage/tamponade)
- Infectious effusion → pericardial drainage (preferably surgically) + systemic antibiotics
- Restrict activity until sx resolve/hsCRP ↓; athletes must also wait 3 mos w/ nl TTE/ECG
- Acute idiopathic pericarditis self-limited in 70–90% of cases
- **Recurrent pericarditis** occurs in ~30% of Pts. Risk factors: subacute, large effusion or tamponade, T >38°C, no NSAID response after 7 d. Rx: colchicine 0.5 mg bid × 6 mo (*Lancet* 2014;383:2232), ? steroids. IL-1 antagonists: anakinra (*JAMA* 2016;316:1906) or rilonacept (*NEJM* 2021;384:31) ↓ risk of recurrence.
- Recurrent effusions: consider pericardial window (percutaneous vs. surgical)

Pericardial Tamponade

Etiology

- Any cause of pericarditis but espec **malignancy**, **infectious**, uremia, ascending AoD, myocardial rupture, periprocedural complication, trauma, post-cardiotomy, idiopathic
- Rapidly accumulating effusions most likely to cause tamponade b/c no time for pericardium to stretch (eg, to ↑ compliance) and accommodate ↑ intrapericardial fluid volume

Pathophysiology (*NEJM* 2003;349:684)

- ↑ intrapericardial pressure, compression of heart chambers, ↓ venous return → ↓ CO
- Diastolic pressures ↑ & equalize in all cardiac chambers → minimal flow of blood from RA to RV when TV opens → blunted *y* descent
- ↑ ventricular interdependence → pulsus paradoxus (pathologic exaggeration of nl physio) Inspiration → ↓ intrapericardial & RA pressures → ↑ venous return → ↑ RV size → septal shift to left. Also, ↑ pulmonary vascular compliance → ↓ pulm venous return. Result is ↓ LV filling → ↓ **LV stroke volume** & blood pressure & pulse pressure.

Clinical manifestations

- **Cardiogenic shock** (hypotension, fatigue) **without pulmonary edema**
- Dyspnea (seen in ~85%) may be due to ↑ respiratory drive to augment venous return

Physical exam (*EHJ* 2014;35:2279)

- **Beck's triad** (present in minority of cases): **distant heart sounds** (28%), ↑ **JVP** (76%) w/ blunted *y* descent, **hypotension** (26%); ± pericardial friction rub (30%)
- Reflex tachycardia (77%), cool extremities
- **Pulsus paradoxus** (Se 82%, Sp 70%) = ↓ SBP ≥10 mmHg during inspiration
  ⊕ LR 3.3 (5.9 if pulsus >12), ⊖ LR 0.03
  Ddx = PE, hypovolemia, severe COPD, auto-PEEP, periconstriction (~1⁄3), RV infarct
  Can be absent if preexisting ↑ LVEDP, arrhythmia, severe AR, ASD, regional tamponade
- Tachypnea and orthopnea but *clear lungs*

Diagnostic studies

- ECG: ↑ HR, ↓ voltage (seen in 42%), electrical alternans (20%), ± signs of pericarditis
- CXR: ↑ cardiac silhouette (89%)
- **Echocardiogram**: ⊕ **effusion**, IVC plethora, **septal shift** with inspiration, **diastolic collapse** of RA (Se 85%, Sp 80%) and/or RV (Se <80%, Sp 90%), **respirophasic Δ's in transvalvular velocities** (↑ across TV & ↓ across MV w/ inspir.), postsurgical tamponade may be localized and not easily visible
- Cardiac cath (right heart and pericardial): elevation (15–30 mmHg) and equalization of intrapericardial and diastolic pressures (RA, RV, PCWP), blunted *y* descent in RA, ↑ in stroke volume postpericardiocentesis is ultimate proof of tamponade
  if RA pressure remains high after drainage, Ddx: effusive-constrictive dis. (visceral pericardium constriction), myocardial. dysfxn (eg, concomitant myocarditis)

Treatment (*EHJ* 2014;35:2279)

- Volume (but be careful b/c overfilling can worsen tamponade) and ⊕ inotropes (avoid βB)
- Avoid vasoconstrictors b/c will ↓ stroke volume & potentially ↓ HR
- Avoid positive pressure ventilation b/c it can further impair cardiac filling (*Circ* 2006;113:1622)
- **Pericardiocentesis** (except if due to aortic/myocardial rupture, for which emergent surgery is treatment of choice; if too unstable, consider small pericardiocentesis to prevent PEA). Watch for pericardial decompression syndrome post-drainage (rare).
- Surgical drainage considered if fluid rapidly reaccumulates, loculated, or hemorrhagic

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Constrictive Pericarditis

Etiology (*Circ* 2011;124:1270)

- Any cause of pericarditis (~1–2% incidence overall after acute pericarditis)
- Highest risk w/ **TB**, **bacterial**, **neoplastic**, **XRT**, connective tissue, postcardiac surgery
- **Viral/idiopathic**, b/c most common cause of pericarditis, also account for signif proportion

Pathophysiology

- Adhesion of visceral and parietal pericardial layers → rigid pericardium that limits diastolic filling of ventricles → ↑ systemic venous pressures
- Venous return is limited only after early rapid filling phase; ∴ rapid ↓ in RA pressure with atrial relaxation and opening of tricuspid valve and *prominent x and y descents*
- Kussmaul sign: JVP does not ↓ w/ inspiration (↑ venous return w/ inspiration, but ⊖ intrathoracic pressure not transmitted to heart b/c of rigid pericardium)

Clinical manifestations (*NEJM* 2011;364:1350)

- Right-sided > left-sided HF (systemic > pulmonary congestion), fatigue, wt loss

Physical exam

- ↑ **JVP** with **prominent *y* descent**, ⊕ **Kussmaul sign** [Ddx: tricuspid stenosis, acute cor pulmonale, RV dysfxn (CMP, RV MI), SVC syndrome]
- Hepatosplenomegaly, ascites, peripheral edema. Consider in Ddx of idiopathic cirrhosis.
- PMI usually not palpable, **pericardial knock** (rare), usually no pulsus paradoxus

Diagnostic studies

- ECG: nonspecific, AF common (up to 33%) in advanced cases
- CXR: calcification (MTb most common), espec in lateral view (although not specific)
- Echocardiogram: ± thickened pericardium, "**septal bounce**" = abrupt displacement of septum during rapid filling in early diastole
- Cardiac catheterization: atria w/ **Ms** or **Ws** (prominent *x* and *y* descents)
  ventricles: **dip-and-plateau** or **square-root sign** (rapid ↓ pressure at onset of diastole, rapid ↑ to early plateau), equalization of RV and LV diastolic pressures
  discordance between LV & RV pressure peaks during respiratory cycle (*Circ* 1996;93:2007)
- CT or **MRI:** thickened pericardium (>4 mm; Se ~80%) w/ tethering (*Circ* 2011;123:e418)

Constrictive Pericarditis vs. Restrictive Cardiomyopathy (*JACC* 2016;68:2329)

Evaluation	Constrictive Pericarditis	Restrictive Cardiomyopathy
Physical exam	⊕ Kussmaul sign Absent PMI ⊕ Pericardial knock	± Kussmaul sign Powerful PMI, ± S_3 and S_4 ± **Murmurs of MR, TR**
ECG	± Low voltage	Low voltage if infiltrative disease ± **Conduction abnormalities**
Echocardiogram	**Respirophasic variation** (25– 40%): inspir. → ↑ flow across TV and ↓ flow across MV e′ (tissue velocity) nl/↑ (>12 cm/sec) **Expir.** hepatic vein flow reversal **Septal bounce in early diastole** Normal wall thickness	<10% respirophasic variation Slower peak filling rate Longer time to peak filling rate **e′** ↓ (<8 cm/sec; 95% Se & Sp) **Inspir.** hepatic vein flow reversal **Biatrial enlargement** ± ↑ wall thickness
CT/MRI	**Usually w/ thickened pericardium**	Normal pericardium
NT-proBNP	Variable	Typically ↑/↑↑ (*JACC* 2005;45:1900)
Cardiac catheterization	Prominent *x* and *y* descents (more so in constriction) Dip-and-plateau sign (more so in constriction)	
	LVEDP = RVEDP RVSP <55 mmHg (Se 90%, Sp 29%) RVEDP >1⁄3 RVSP (Se 93%, Sp 46%) **Discordance** of LV & RV pressure peaks during respiratory cycle **Systolic area index** (ratio of RV to LV pressure–time area in inspir vs. expir) >1.1 (Se 97%, Sp 100%)	**LVEDP** > **RVEDP** (esp. w/ vol.) RVSP >55 mmHg RVEDP <1⁄3 RVSP Concordance of LV & RV pressure peaks during respiratory cycle Systolic area index ≤1.1 (*JACC* 2008;51:315)
Endomyocardial biopsy	Usually normal	± **Specific etiology of RCMP** (fibrosis, infiltration, hypertrophy)

Treatment

- Diuresis if intravascular volume overload; surgical pericardiectomy (*JACC* 2024;84:561) if infectious or advanced; anti-inflammatory therapy (eg, NSAIDs, colchicine) if inflammatory

HYPERTENSION

ACC/AHA Classification for Office-Based BP (Reprinted with permission from *HTN* 2018;71:e13)		
Category	**Systolic (mmHg)**	**Diastolic (mmHg)**
Normal	<120	<80
Elevated	120–129	<80
Stage 1 hypertension	130–139	80–89
Stage 2 hypertension	≥140	≥90

Avg ≥2 measurements on ≥2 occasions. If disparity in category between SBP & DBP, go w/ higher stage. Confirm ↑ office BP with out-of-office (ABPM or home cuff); Rx stage 2 immed. White coat HTN (≥stage 1 in office but < at home) at ↑ risk of HTN. Masked (<Stage 1 in office but ≥ at home), if persist, Rx. HTN in preg: ≥140/90.

Epidemiology (*JAMA* 2022;328:1849)

- Prevalence 47% in U.S. adults, higher in African Americans; M = F
- Of those with HTN, ~40% unaware of dx; of those dx w/ HTN, <½ achieve target BP

Etiologies (*JACC* 2022;80:1480)

- **Essential** (95%): onset 25–55 y; ⊕ FHx. Unclear mechanism but interplay of ↓ vascular compliance and microvasc renal injury over time → hyperactive sympathetics.
- **Secondary:** Consider if Pt <20 or >50 y or if sudden onset, severe, refractory HTN

Secondary Causes of Hypertension			
Diseases		**Suggestive Findings**	**Initial Workup**
RENAL	**Renal parenchymal** (2–3%)	h/o DM, polycystic kidney disease, glomerulonephritis	CrCl, albuminuria See “Kidney Disease”
	Renovascular (1–2%) Athero (90%) FMD (10%, young women) PAN, scleroderma	ARF induced by ACEI/ARB Recurrent flash pulm edema Renal bruit; hypokalemia (*NEJM* 2009;361:1972)	MRA (>90% Se & Sp, less for FMD), CTA, duplex U/S, angio, plasma renin (low Sp)
ENDO	**Hyperaldo or Cushing’s** (1–5%)	Hypokalemia Metabolic alkalosis	See “Adrenal Disorders”
	Pheochromocytoma or paraganglioma (<1%)	Paroxysmal HTN, H/A, palp.	
	Myxedema (<1%)	See “Thyroid Disorders”	TFTs

	Hypercalcemia (<1%)	Polyuria, dehydration, Δ MS	iCa
OTHER	**Obstructive sleep apnea** (qv); alcohol		
	Medications: OCP, steroids, licorice; NSAIDs (espec COX-2); Epo; CsA; TKI; EtOH		
	Aortic coarctation: ↓ LE pulses, systolic murmur, radial–femoral delay; abnl TTE, CXR		
	Polycythemia vera: ↑ Hct		

Standard workup (*JAMA* 2021;325:1650 & 326:339)

- Goals: (1) identify CV risk factors; (2) consider 2° causes; (3) assess for target-organ damage
- History: CAD, HF, TIA/CVA, PAD, DM, renal insufficiency, OSA, preeclampsia or HELLP; ⊕ FHx for HTN; diet, Na intake, smoking, alcohol, prescription and OTC meds, OCP
- Physical exam: ✓ **BP in both arms;** funduscopic exam, BMI, cardiac (LVH, murmurs), vascular (bruits, radial–femoral delay), abdominal (masses or bruits), neuro exam
- Testing: K, BUN, Cr, Ca, glc, Hct, U/A, lipids, TSH, urinary albumin:creatinine (if ↑ Cr, DM, peripheral edema), renin/aldo, ECG (for LVH), CXR, TTE (eval for valve abnl, LVH)
- Ambulatory BP monitoring (ABPM): consider for episodic, masked, resistant, or white coat HTN; stronger predictor of mortality than clinic BP (*NEJM* 2018;378:1509); 24 h target <130/80

Complications of HTN

- Neurologic: **TIA/CVA**, ruptured aneurysms, vascular dementia
- Retinopathy: stage I = arteriolar narrowing; II = copper-wiring, AV nicking; III = hemorrhages and exudates; IV = papilledema
- Cardiac: **CAD**, **LVH**, **HF, AF**
- Vascular: aortic dissection, aortic aneurysm (HTN = key risk factor for aneurysms)
- Renal: proteinuria, **renal failure**

Treatment (*Circ* 2018;138:e426; *NEJM* 2018;378:636)

- In general, goal <**130/80 mmHg**
- In high CV risk, SBP 120's vs. 130–140 mmHg ↓ MACE, but w/ ↑ HoTN, AKI, syncope, electrolyte abnl (*NEJM* 2021;384:1921 & 385:1268; 2025;392:1155; *Lancet* 2024;404:245)
- Every ↓ 5 mmHg → ~10% ↓ ischemic heart disease, stroke, and HF (*Lancet* 2021;397:1625)
- **Lifestyle modifications** (each may ↓ SBP ~5 mmHg)
  weight loss: goal BMI 18.5–24.9; aerobic exercise: ≥75 (high) or 150 (moderate) min/wk
  diet: rich in fruits & vegetables, low in saturated & total fat (DASH, *NEJM* 2001;344:3)
  ↓ Na: ≤1.5 g/d or ↓ 1 g/d; salt substitute w/ KCl (*NEJM* 2021;385:1067; *JAMA* 2023;330:2258)
  limit alcohol: ≤2 drinks/d in men; ≤1 drink/d in women & lighter-wt Pts; avoid NSAIDs
- **Pharmacologic options**
  Initiate BP med if BP ≥130/80 & *either* clinical ASCVD, HF, CKD, T2DM, ≥65 yrs old *or* 10-y ASCVD risk ≥10%; otherwise, if BP ≥140/90; elderly, as tolerated (*EHJ* 2024;45:3912)
  Uncomplicated: CCB, ARB/ACEI, or thiazide (chlorthalidone preferred) are 1st line; βB not. For Black Pts, reasonable to start with CCB or thiazide.
  + **CAD**: ACEI or ARB; ACEI+CCB superior to ACEI+thiazide (*NEJM* 2008;359:2417) or βB+diuretic (*Lancet* 2005;366:895); may require βB and/or nitrates for anginal relief; if h/o MI, ACEI/ARB ± aldo antag ± βB (see "ACS")
  + **HF:** RASi, βB, diuretics, MRA (& SGLT2i) (*Circ* 2019;139:2089)
  + **prior stroke:** ACEI ± thiazide (*Lancet* 2001;358:1033)
  + **diabetes mellitus:** ACEI or ARB; ± SGLT2i; can also consider thiazide or CCB
  + **chronic kidney disease:** ACEI or ARB (*NEJM* 2001;345:851 & 861); SGLT2i
- Tailoring therapy: if stage 1, start w/ monoRx; if stage 2, consider starting w/ combo; start at ½ max dose; after ~1 mo, uptitrate or add drug. Fixed-dose quadruple ¼ dose combo achieved 7 mmHg lower SBP than max dose ARB monoRx (*Lancet* 2021;398:1043).

- Self-measured home BP monitoring improves BP control (*Circ* 2020;142:e42)
- **Pregnancy:** methyldopa, labetalol, & nifed preferred.; avoid diuretics; Ø ACEI/ARB/aldo antag (*JACC* 2019;73:457). Target <140/90 (*NEJM* 2022;386:1781).

Resistant HTN (BP above goal despite ≥3 drugs incl diuretic; *HTN* 2018;72:e53)

- Exclude: 2° causes (see table) and *pseudoresistance:* inaccurate measure (cuff size), diet noncomp (↑ Na), poor Rx compliance/dosing, white coat HTN (✓ ABPM)
- Ensure effective diuresis (chlorthalidone or indapamide > HCTZ; loop > thiazide if eGFR <30)
- Can add aldosterone antagonist (*Lancet* 2015;386:2059), βB (particularly vasodilators such as carvedilol or labetalol), α-blocker, or direct vasodilator. Aprocitentan (endothelin-1 blocker) ↓ SBP by ~4 mmHg; side effect is fluid retention w/ edema (*Lancet* 2022;400:1927).
- **Renal denervation (RDN)**: catheter-based RF or U/S ablation of renal nerves to modify sympathetic outflow. Overall ~5–10 mmHg ↓ in BP in 24-hr or ambulatory SBP (*Lancet* 2021;397:2476; 2022;399:1401 & 2022;400:1405; *HTN* 2024;81:e135).

Hypertensive Crises

- **Hypertensive emergency:** ↑ BP (usually SBP >180 or DBP >120) → target-organ damage
  Neurologic damage: encephalopathy, hemorrhagic or ischemic stroke, papilledema
  Cardiac damage: ACS, HF/pulmonary edema, aortic dissection
  Renal damage: proteinuria, hematuria, acute renal failure; scleroderma renal crisis
  Microangiopathic hemolytic anemia; preeclampsia–eclampsia
- **Severe asymptomatic HTN:** SBP >180 or DBP >120 (? 110) w/o target-organ damage

Precipitants

- Progression of essential HTN ± medical noncompliance (espec clonidine) or Δ in diet
- Progression of renovascular disease; acute glomerulonephritis; scleroderma; preeclampsia
- Endocrine: pheochromocytoma, Cushing's
- Sympathomimetics: cocaine, amphetamines, MAO inhibitors + foods rich in tyramine

Treatment tailored to clinical condition (*Circ* 2018;138:e426)

- AoD, eclampsia/severe preeclampsia, pheo: target SBP <140 (<120 for AoD) in **1 hour**
- Emerg w/o above: ↓ BP by ~25% in 1 h; to 160/100–110 over next 2–6 h, then nl over 1–2 d
- Acute ischemic stroke (w/in 72 hr from sx onset): <185/110 before lysis initiated, o/w target <220/120 (same SBP goal for ICH)
- Watch UOP, Cr, mental status: may indicate a lower BP is not tolerated

IV Drugs for Hypertensive Crises (*Circ* 2018;138:e426; *Stroke* 2018;49:46)

Drug	Dose	Preferred for
Labetalol	20–80 mg IVB q10min or 0.4–2 mg/min	AoD, ACS, Stroke, Eclampsia
Esmolol	0.5–1 mg/kg load → 50–200 µg/kg/min	AoD, ACS
Nitroprusside*	0.25–10 µg/kg/min	Pulm edema
Nitroglycerin	5–500 µg/min	Pulm edema, ACS
Nicardipine	5–15 mg/h (can ↑ 2.5 mg/h q5min)	Stroke, AKI, Eclampsia, Pheo
Clevidipine	1–32 mg/h (can titrate q5–10min)	Stroke, Pulm edema, AKI, Pheo
Fenoldopam	0.1–1.6 µg/kg/min	AKI
Hydralazine	10–20 mg q20–30min prn	Eclampsia

Phentolamine	5–15 mg bolus q5–15min	Pheo

*Metabolized to cyanide → Δ MS, lactic acidosis, death. Limit use of very high doses (8–10 µg/kg/min) to <10 min.

- Severe asx HTN: goal to normalize BP over hrs to days. Reinstitute/intensify anti-HTN Rx. IV option: enalaprilat 1.25–5 mg q6h. Other PO options: labetalol 200–800 mg q8h, captopril 12.5–100 mg q8h, hydral 10–75 mg q6h, clonidine 0.2 mg load → 0.1 mg q1h.

AORTIC ANEURYSMS

Definitions (*Circ* 2022;146:e334)

- ≥50% dilation of all 3 layers; in root & ascending, 4.0-4.4 cm = dilated; ≥4.5 cm = aneurysm
- **Location**. Thoracic aortic aneurysms (TAA): root, ascending, arch, descending. Abdominal aortic aneurysms (AAA): abdominal aorta (mostly infrarenal).

Epidemiology

- **TAA:** 5–10/100,000 Pt-yrs; ~60% root and/or ascending, 30% descending, <10% arch
- **AAA:** ~4–8% prev in those >60 y; ~5× more common in ♂

Pathophysiology & risk factors (*JACC* 2020;76:201 & 2021;78:201; *Circ* 2022;146:e334)

- Medial degen and/or ↑ wall stress; wall stress ∝ [(ΔP × r) / (wall thickness)] (Laplace's law)
- **Clinical risk factors:** HTN, smoking, HLD, older age, ♂ sex (AAA)
- **Genetic**: syndromic (vide infra) & nonsyndromic causes of TAA Marfan (*FBN1*): ectopia lentis, tall stature, arachnodactyly, pectus deformities Loeys–Dietz (*TGFBR1/2*): hypertelorism, bifid uvula, hyperlucent skin, bluish sclera Ehlers–Danlos (*COL3A1*): easy bruising, translucent skin, uterine or intestinal rupture
- **Congenital**: bicuspid AoV (BAV), Turner, coarctation, complex CHD
- **Aortitis**: GCA, Takayasu, spondyloarthritis, IgG4, Behçet's, infective (eg, syphilis)

Screening (*Circ* 2022;146:e334)

- **TAA:** if BAV or 1° relative w/: (a) TAA, dissection, or BAV; or (b) genetic syndrome
- **AAA:** ✓ for pulsatile abd mass; U/S ♂ (consider for ♀) 65–75 y w/ prior tobacco or FHx

Clinical manifestations

- **Pain:** gnawing chest, back, or abdominal pain; new or worse pain may signal rupture
- **Rupture:** risk ↑ w/ diameter, rapid growth, CTD, genetic aortopathy, ♀, smoking, HTN
  TAA: ~2.5%/yr if <6 cm vs. 7%/yr if >6 cm; AAA: ~1%/yr if <5 cm vs. 6.5%/yr if 5–5.9 cm
  rupture p/w severe constant pain and hemorrhagic shock; ~80% mortality at 24 hrs
- Aortic insufficiency (TAA), CHF, acute aortic syndromes (qv)
- Thromboembolic ischemic events: CNS, viscera, extremities
- Compress/impinge on structures (eg, SVC, trachea, esophagus, laryngeal nerve)

Diagnostic studies (*JACC* 2020;76:201)

- **Contrast CT:** quick, noninvasive, high Se & Sp for all aortic aneurysms
- **TTE/TEE:** TTE useful for root and proximal Ao; TEE is invasive but see other parts of TAA
- **MRI:** favored over CT for root, valve eval, useful in AAA; ↑ time and less available
- **Abdominal U/S:** screening/surveillance test of choice for infrarenal AAA

Follow-up (*Circ* 2022;146:e334)

- Typical expansion rates: ~0.05 cm/y for TAA, ~0.26 cm/y for AAA
- **TAA**: 6 mo after dx; if stable, q6–24 mos depending on diameter
- **AAA**: q3y for <4 cm; q1y for ♂ 4–4.9 cm/♀ 4–4.4 cm; q6m for ♂ ≥5 cm/♀ ≥4.5 cm
- Screen for CAD, PAD, & aneurysms elsewhere, espec popliteal. ~25% of Pts w/ TAA will also have AAA, and 25% of AAA Pts will have a TAA: consider pan-Ao imaging.

Treatment (*NEJM* 2021;385:1690; *Circ* 2022;146:e334)

- Goal is to prevent rupture by modifying risk factors
- **Risk factor modification:** smoking cessation, statin (LDL-C <70 mg/dL), consider ASA
- **BP control** (goal BP <120–130/80): 1st line β**B** (↓ dP/dt, ↓ growth); **ARB** (esp in Marfan)
- Low-intensity CV exercise OK, no burst activity w/ Valsalva maneuvers (eg, heavy lifting)
- **Indications for intervention:** sx, size, speed of progression
  - **Marfan or other heritable:** ≥4.5–5.0 cm (depending on RF's and experience of team)
  - **Sporadic or BAV:** ≥5.0–5.5 cm
  - **TAA** rapid growth: ≥0.3 cm/y in 2 consecutive yrs or ≥0.5 cm in 1 yr
  - **TAA Desc:** ≥5.5 cm
  - **AAA:** ≥5.5 cm ♂ or ≥5.0 cm ♀; ↑ ≥0.5 cm/6 mos; inflamm/infection

Surgery & endovascular repair (EVAR) (*Circ* 2022;146:e334)

- **Surgery:** resection & replacement w/ graft. If involves root, also address AoV & coronaries.
- **EVAR:** less morbid but requires favorable anatomy including reasonable landing zones
- **TEVAR** (thoracic EVAR) recommended over open technique if CTD w/ favorable anatomy & descending TAA needing repair; otherwise, shared decision
- **AAA:** EVAR or open repair in good surg candidates; EVAR ↓ short-term mort., bleeding, LOS; but long-term graft complic. (3–4%/y; endoleak, need for reintervention, rupture) necessitate periodic surveillance, with no difference in mortality long term, except ? in those <70 y (*Lancet* 2016;388:2366; *NEJM* 2019;380:2126)
- **Ruptured AAA**: EVAR preferred to open repair (*J Vasc Surg* 2018;67:2)
- **Endoleak**: EVAR complication; five types; may occur early or late

ACUTE AORTIC SYNDROMES

Definitions (*Circ* 2022;146:e334)

- **Aortic dissection:** intimal tear → blood extravasates into Ao media (creates false lumen)
- **Intramural hematoma**: vasa vasorum rupture → medial hemorrhage that does not → Ao
- **Penetrating Ao ulcer (PAU):** athero plaque penetrates intima → medial hemorrhage

Classification (proximal more common than distal; *JACC* 2019;74:1494 & 2020;76:1703)

- **Type A** = **proximal:** involves ascending Ao, regardless of origin
- **Type B** = **distal:** involves descending Ao only, distal to L subclavian artery

Risk factors (*Lancet* 2015;385:800; *Circ* 2022;146:e334)

- **Classic**: **HTN** (>70% of dissections); **age** (50s–70s), ♂ **sex**, **smoking**
- **Genetic:** *CTD* (Marfan, Loeys–Dietz, Ehlers–Danlos type IV); *congenital anomaly* (bicuspid AoV, coarct [eg, Turner's syndrome], PCKD); FHx (AoD or aneurysm in 1st-degree relative)

- **Acquired:** *aortitis* (Takayasu's, GCA, Behçet's, syphilis); *preg.* (typically 3rd trim.); FQ use
- **Rapid Ao diameter expansion:** growth ≥0.5 cm/yr
- **Acute precipitants:** ↑↑ **BP** (including cocaine, Valsalva [eg, lifting]); **trauma:** blunt, decel. injury (eg, MVA); cath, IABP, Impella, cardiac/Ao surgery

Clinical Manifestations and Physical Exam* (*JAMA* 2000;283:897)		
Feature	**Proximal**	**Distal**
"Aortic" pain (abrupt, severe, tearing or ripping quality, *maximal at onset* [vs. crescendo for ACS])	**94%** (chest, back)	**98%** (back, chest, abd)
Syncope (often due to tamponade)	**13%**	4%
HF (usually due to acute AI)	**9%**	3%
CVA	**6%**	2%
HTN	36%	**70%**
HoTN or shock (tamponade, AI, MI, rupture)	**25%**	4%
Pulse deficit (if involves carotid, subclavian, fem)	**19%**	**9%**
AR murmur	**44%**	12%

*S/S correlate w/ affected branch vessels & distal organs; may Δ as dissection progresses

Initial evaluation & diagnostic studies (*Circ* 2022;146:24)

- **H&P**: incl. bilat BP & radial pulses for symmetry; ECG w/ STE if propagates to coronaries
- CXR: abnl in 60–90% [↑ mediast. (absence ⊖ LR 0.3), L pl effusion] but *cannot* r/o AoD
- **CT:** preferred as quick & available; see entry point, extent, & complications; Se & Sp ≥93%
- **MRI:** Se & Sp >98%, but time-consuming & not readily available
- **TEE:** Se >95% prox, 80% for distal; can assess cors/peric/AI; "blind spot" behind trachea
- ⊖ Initial imaging but high clinical suspicion → further studies (*2/*3 w/ AoD have ≥2 studies)
- **D-dimer** <500 ng/mL has Se/NPV ~97%, Sp ~50%, *but not if high risk* and not for IMH
- **Risk scores:** ADD-RS (0–3): risk factor; Ao pain; perf. deficit, AI, or shock. >1→ image; ≤1 & DD <500 = NPV >99% (*Circ* 2018;137:250). AORTAs: 1 pt each for: sudden-onset pain, severe pain, neuro deficit, pulse deficit, aneurysm; 2 pts HoTN/shock. ≥2 = high prob.

Treatment (*Circ* 2022;146:e334; *Lancet* 2023;401:773)

- ↓ **dP/dt** targeting HR 60–80 & central BP <120 (or lowest preserving perfusion); r/o pseudo-hypotension (ie, subclavian dissection → ↓ arm BP; use highest BP & place a-line)
- ***First* IV βB** (eg, esmolol, labetalol) to blunt reflex ↑ HR & inotropy response to vasodilators; non-DHP CCB if βB contraindic; ***then* ↓ *SBP w/* IV vasodilators** (eg, nitroprusside); Rx pain
- **If HoTN:** urgent surgical consult, IVF to achieve euvolemia, pressors to keep MAP 60–65 mmHg; r/o complication (eg, tamponade, contained rupture, severe AI)
- **Type A:** surg consult in **all acute (<15 d)** and in chronic if c/b progression, AI or aneurysm
- **Type B:** med Rx unless complic. (below) or high risk of adverse remodeling. EVAR may incl. fenestration to decompress false lumen, open occluded branch or stent entry tear.

Complications (occur in ~20%; *Circ* 2022;146:e334)

- *Freq assess (sx, BP, UOP), pulses, labs (Cr, Hb, lactic acid), imaging (~7 d or sooner if Δs)*
- *Uncontrolled BP or persistent pain may indicate complication/extension*
- **Progression:** propagation of dissection, ↑ aneurysm/false lumen size
- **Rupture:** pericardial sac → tamponade (avoid pericardiocentesis unless PEA); blood in pleural

space, mediast., retroperitoneum; ↑ in hematoma on imaging portends rupture
- **Malperfusion** (partial or complete obstruction of branch artery; can be *static* or *dynamic*) *coronary* → MI (usually RCA → IMI b/c dissection follows outer Ao curvature); *innominate/carotid* → CVA, Horner; *intercostal/lumbar* → spinal cord ischemia/paraplegia; *innominate/subclavian* → upper ext ischemia; *iliac* → lower ext ischemia; *celiac/mesenteric* → bowel ischemia; *renal* → AKI or slow ↑ Cr, refractory HTN
- **AI:** due to annular dilatation or disruption or displacement of leaflet by false lumen
- **Mortality. Type A:** early 1–2%/hr; 57% w/ med Rx alone, 18% w/ surg. **Type B:** 10–20%.

ARRHYTHMIAS

Bradycardias, AV Block, and AV Dissociation

Sinus bradycardia (SB, <50–60 bpm) (*NEJM* 2000;342:703; *Circ* 2019;140:e382)

- Etiologies: **meds** (incl βB, CCB, amio, Li, dig), ↑ **vagal tone** (incl. athletes, sleep, IMI), **metabolic** (hypoxia, sepsis, myxedema, hypothermia, ↓ glc), OSA, ↑ ICP
- Treatment: if no sx, none; if symptomatic, atropine, β_1 agonists (short-term) or pacing
- Most common cause of sinus pause is *blocked premature atrial beat*

Tachycardia–bradycardia ("tachy-brady") syndrome

- Features may include: periods of unprovoked SB, SA arrest, paroxysms of SB and atrial tachyarrhythmias, chronotropic incompetence w/ ETT
- Treatment: meds alone usually fail (adeq. control tachy → unacceptable brady); usually need **combination of meds** (βB, CCB, dig) for tachycardia & **PPM** for bradycardia

AV Block (*Circ* 2019;140:e382)	
Type	**Features**
1°	Prolonged PR (>200 ms), all atrial impulses conducted (1:1)
2° Mobitz I (Wenckebach)	Progressive ↑ PR until impulse not conducted (→ "grouped beating") **AV node** pathology: ischemia (IMI), inflammation (myocarditis, endocarditis, MV surgery), high vagal tone (athletes), drug induced Classically (~50%), absolute ↑ in PR *decreases* over time (→ ↓ RR intervals, duration of pause <2× preceding RR interval); nl QRS AVB usually worsens w/ carotid sinus massage, improves w/ atropine Often paroxysmal/nocturnal/asx, no Rx required
2° Mobitz II	Blocked impulses w/ consistent PR interval, often prolonged QRS **His-Purkinje** pathology: ischemia (AMI), degeneration of conduction system, infiltrative disease, inflammation AVB may improve w/ vagal maneuvers, may worsen w/ atropine May progress to 3° AVB. Pacing pads, transven. pacing often required.
3° (complete)	No AV conduction. Escape, if present, narrow (jxnal) or wide (vent.).

If 2:1 block, cannot distinguish type I vs. II 2° AVB (no chance to observe PR prolongation); usually categorize based on other ECG & clinical data. High-grade AVB usually refers to block of ≥2 successive P waves.

AV dissociation

- *Default:* slowing of SA node allows subsidiary pacemaker (eg, AV junction) to take over

- *Usurpation:* acceleration of subsidiary pacemaker (eg, AV junctional tach, VT)
- *3° AV block:* atrial pacemaker unable to capture ventricles, subsidiary pacemaker emerges; distinguish from *isorhythmic dissociation* (A ≈ V rate, some P waves nonconducting)

Temporary pacing wires

- Consider w/ bradycardia with hemodynamic instability or unstable escape rhythm when perm pacer not readily available. Risks: infxn, RV perf, VT, PTX, CHB if existing LBBB.
- Consider instead of PPM for sx brady from reversible cause (βB/CCB O/D, Lyme, SBE, myocarditis, s/p cardiac surgery/trauma/TAVR), TdP, acute MI (sx brady/high-grade AVB)

Supraventricular Tachycardias (SVTs)

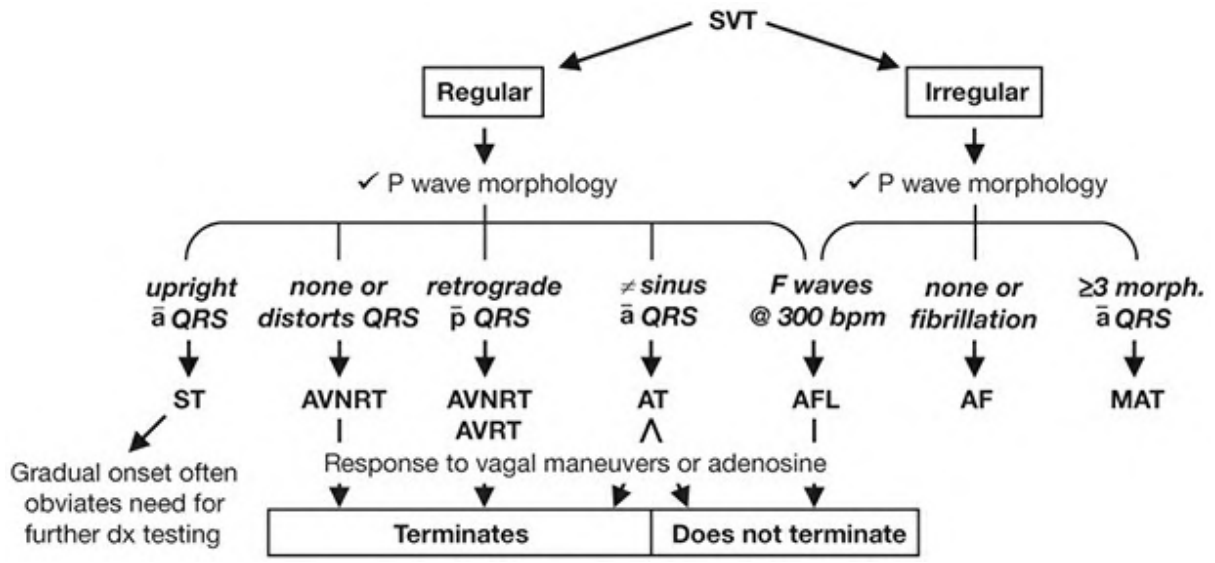
*Arise above ventricles, ∴ **narrow QRS** unless aberrant conduction, pre-excitation, or V-pacing*

Common Etiologies of SVT (*JAMA* 2024;331:601)		
	Type	**Features**
Atrial	Sinus tachycardia (ST)	Caused by pain, fever, hypovolemia, hypoxia, PE, anemia, anxiety, withdrawal, β-agonists, etc.
	Atrial tachycardia (AT)	Originates at site in atria other than SA node. Seen w/ CAD, COPD, ↑ catechols, EtOH, dig.
	Multifocal atrial tachycardia (MAT)	↑ automaticity at multiple sites in the atria; seen with underlying pulmonary disease (eg, COPD)
	Atrial flutter (AFL)	Clockwise or counterclockwise macroreentry, usually w/in right atrium (cavotricuspid isthmus)
	Atrial fibrillation (AF)	Chaotic atrial activation with rapid, irregular AVN bombardment; often from pulmonary veins
AV Jxn	AV nodal reentrant tach (AVNRT)	Reentrant circuit using dual pathways w/in AVN
	Atrioventricular reciprocating tachycardia (AVRT)	Reentry using AVN & access. path. May show pre-excitation (WPW) or not (concealed access. path.). Can be ortho or antidromic (vide infra).
	Nonparoxysmal junctional tachycardia (NPJT)	↑ jxnal automaticity. May see retro. P, AV dissoc. A/w myo/endocarditis, cardiac surg, IMI, dig.

Diagnosis of SVT Type (*JAMA* 2024;331:601)	
Onset	Abrupt on/off argues against sinus tachycardia
Rate	Not dx b/c most can range from 140 to 250 bpm, *but:* ST usually <150; AFL often conducts 2:1 → vent. rate 150; AVNRT & AVRT usually >150
Rhythm	Irregular → AF, AFL w/ variable block, or MAT
P-wave morphology	Before QRS (ie, long RP) → ST, AT (P ≠ sinus), MAT (≥3 morphologies) None (ie, buried in or deforming terminal QRS, eg, pseudo-RSR′ in V_1) → typical AVNRT, NPJT, fine AF After QRS (ie, short RP) & inverted in inf. leads (ie, *retrograde* atrial) → AVNRT, AVRT (usually slightly after QRS; RP interval >100 ms favors AVRT over AVNRT), or NPJT

	Fibrillation or no P waves → AF *Saw-toothed "F" waves* (best seen in inferior leads & V_1) → AFL
Response to vagal stim. or adenosine	Slowing of HR often seen with ST, AF, AFL, AT, whereas reentrant rhythms (AVNRT, AVRT) may abruptly terminate (classically w/ P wave after last QRS) or no response. Occ AT may terminate. In AFL & AF, ↑ AV block may unmask "F" waves or fibrillation

Figure 1-3 Approach to SVT (adapted from *NEJM* 2012;367:1438)



Treatment of Stable SVT (*JACC* 2016;67:e27; *JAMA* 2024;331:601)		
Rhythm	**Acute Treatment**	**Long-Term Treatment**
ST	Treat underlying stressor(s)	n/a
AT	βB, CCB, or amiodarone; ? vagal maneuvers or adenosine	radiofrequency ablation (RFA); βB or CCB, ± class IC/III AAD
AVNRT or AVRT	**Vagal man.; adenosine** (caution in AVRT*) **CCB/**βB, DCCV if needed	*For AVNRT (see next section for AVRT):* **RFA**; CCB or βB, ± Class IC (if nl heart)
AF	**βB, CCB, digoxin, AAD**	See "Atrial Fibrillation"
AFL	**βB, CCB, AAD**	RFA; βB or CCB ± AAD
MAT	CCB or βB if tolerated	Treat underlying disease. CCB or βB. AVN ablation + PPM if refractory to meds

*Avoid adenosine & nodal agents if accessory pathway + pre-excited tachycardia, vide infra (*Circ* 2014;130:e199)

- *Catheter ablation:* high overall success rate (AFL/AVNRT ~95%, AVRT ~90%, AF ~70%) complications: stroke, MI, bleeding, perforation, conduction block

Accessory Pathways (Wolff–Parkinson–White)

Definitions

- **Accessory pathway** (bypass tract) of conducting myocardium connecting atria & ventricles,

allowing impulses to bypass normal AVN delay

- **Pre-excitation (WPW) pattern:** ↓ PR interval, ↑ QRS width w/ δ wave (slurred onset, can be subtle). ST & Tw abnl (can mimic old IMI).
  Only seen w/ pathways that conduct antegrade (if pathway only conducts retrograde, then ECG will be normal during SR; "concealed" bypass tract)
- **WPW syndrome:** WPW accessory pathway + paroxysmal tachycardia

Classic tachycardias of WPW accessory pathways

- **Orthodromic AVRT:** *narrow-complex* SVT (typically), conducting ↓ AVN & ↑ accessory pathway; requires retrograde conduction and ∴ can occur w/ concealed bypass tracts
- **Antidromic AVRT** (rare): *wide-complex* SVT, conducting ↓ accessory pathway & ↑ AVN; requires antegrade conduction and ∴ should see pre-excitation pattern during SR
- **AF** w/ rapid conduction down accessory pathway; ∴ wide-complex irregular SVT; requires antegrade conduction; ∴ should see pre-excitation in SR. Rarely can degenerate into VF.

Treatment (*Heart Rhythm* 2012;9:1006, *Circ* 2014;130:e199 & 2016;133:e506)

- **AVRT** (orthodromic): vagal, βB, CCB; care w/ adenosine (can precip AF); *have defib ready*
- **AF/AFL** w/ conduction down accessory pathway: need to Rx arrhythmia *and* ↑ pathway refractoriness. Use **procainamide**, **ibutilide**, or DCCV; ***avoid*** CCB, βB, amio, dig, & adenosine, b/c can ↓ refractoriness of pathway → ↑ vent. rate → VF (*Circ* 2016;133:e506).
- **Long term:** RFA if sx; if not candidate for RFA, then AAD (IA, IC) or CCB/βB
  Consider RFA if asx but AVRT or AF inducible on EPS (*NEJM* 2003;349:1803) or if rapid conduction possible (✓ w/ EPS if pre-excitation persists during exercise testing)
  Risk of SCD related to how short RR interval is in AF (eg, <250 ms) and if SVT inducible

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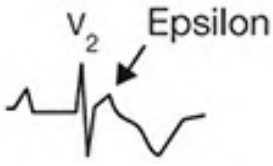
Wide-Complex Tachycardias (WCTs)

Etiologies (*Lancet* 2012;380:1520)

- **Ventricular tachycardia (VT):** accounts for 80% of WCT in unselected population
- **SVT conducted with aberrancy:** either fixed BBB, rate-dependent BBB (usually RBBB), conduction via an accessory pathway, or atrially triggered ventricular pacing

Monomorphic ventricular tachycardia (MMVT)

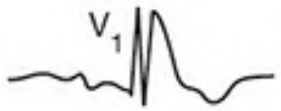
- All beats look similar; predominantly upward in V_1 = RBBB-type vs. downward = LBBB-type
- Most commonly in obviously *structurally abnormal* heart: **prior MI** (scar) or **CMP**
- May occur in *apparently nl heart that is actually diseased:* **subtle HCM**, **infiltrative CMP, myocarditis, arrhythmogenic (RV) CMP**: incomplete RBBB
  ε wave (terminal notch in QRS) & TWI in V_1–V_3, LBBB-type VT,
  dx w/MRI/TTE (*Heart Rhythm* 2019;16:11:e311)



- Can occur in structurally *normal* heart w/ nl resting ECG & cardiac MRI:
  RVOT (LBBB-type) **or LVOT (RBBB-type) VT:** VT or PVCs w/ inf. axis; CCB/βB or ablate
  Left posterior fascicle region ("fascicular" VT): RBBB in V_1, superior axis; often confused for SVT w/ aberrancy; verapamil-sensitive

Polymorphic ventricular tachycardia (PMVT)

- QRS morphology and/or axis changes from beat to beat
- Etiologies: **ischemia; CMP; catecholaminergic (CPVT)**
  - **torsades de pointes** (TdP = "twisting of the points," PMVT + ↑ QT): ↑ QT ***acquired*** (meds, lytes, stroke, see "ECG") w/ risk ↑ w/ ↓ HR, freq PVCs (pause dependent) ***or congenital*** (K/Na channelopathies) w/ resting Tw abnl & TdP triggered by sympathetic stimulation (eg, exercise, emotion, sudden loud noises) (*Lancet* 2008;372:750)
  - Brugada syndrome (Na channelopathy; *JACC* 2018;72:1046): ♂ >> ♀; pseudo-RBBB w/ STE in V_1–V_3 on resting ECG. ECG Δs provoked w/ class IA/IC. Rx: quinidine, possibly ablation (*Circ* 2023;147:1568), and ICD.



Diagnostic clues that favor VT (assume VT until proven o/w)

- **Prior MI** or **LV dysfxn** *best predictors* that WCT is VT; hemodynamics & rate not reliable
- MMVT is regular, but initially it may be slightly irregular, mimicking AF w/ aberrancy; *grossly* irregularly irregular rhythm suggests AF w/ aberrancy or pre-excitation
- ECG features that favor VT (*Circ* 2016;133:e506)
  - *AV dissociation* (independent P waves, capture or fusion beats) proves VT;
  - *Very wide QRS* (>140 ms in RBBB-type or >160 in LBBB-type); *extreme axis deviation*
  - *QRS morph. atypical for BBB* (longest precordial onset R to nadir S >100 ms & R wider than S) RBBB-type: absence of tall R′ (or presence of monophasic R) in V_1, r/S ratio <1 in V_6
  - LBBB-type: onset to nadir ≥60 ms in V_1, q wave in V_6
  - *Initial R wave in aVR; concordance* (QRS in all precordial leads w/ same pattern/direction)

Management of VT (*EHJ* 2015;36:2793; *Circ* 2018;138:e272; *NEJM* 2019;380:1555)

- Workup: **echo** to ✓ LV fxn, **angio** or **stress test** to r/o ischemia, ? MRI and/or RV bx to look for infiltrative CMP or ACM, ? **EP study** to assess for VT in Pts w/o ICD indication
- **ICD:** 2° prevention for VT/VF arrest (unless due to reversible cause) or cardiac syncope with inducible VT on EP study. 1° prev. if high risk, eg, EF <30–35% (>40 d after MI, >90 d after revasc), ACM, ? Brugada, certain LQTS, severe HCM. See "Cardiac Rhythm Mgmt Devices." Consider wearable vest if reversible or waiting for ICD (*NEJM* 2018;379:1205). Antitachycardia pacing (ATP = burst pacing faster than VT) can terminate VT w/o shock.
- **Meds:** βB, antiarrhythmics (eg, amio, sotalol, mexiletine, quinidine); verapamil if fascicular VT
- If med a/w TdP → QT >500 ± PVCs: d/c med, replete K, give Mg, ± pacing
- **Ablate:** if isolated VT focus, breakthrough on or escalation of AADs, or if recurrent ICD firing. Also consider in ischemic CMP w/ ICD & recurrent VT (*NEJM* 2025;392:737).
- **VT storm** (≥3 episodes w/in 24 h): AADs (βB, amio, lidocaine, procainamide); intubation & sedation; consider stellate ganglion block. Catheter ablation when stable.
- **Rx-refractory:** optimize HF GDMT as indicated; max AAD; consider epicardial ablation (if not yet done) or stereotactic (*Circ Arrhythmia* 2022;15:e010955). Evaluate for heart transplant.

ATRIAL FIBRILLATION

Classification (*Circ* 2024;149:e1)

- **Pre-AF:** structural (eg, LA enlargement) or electrical (frequent atrial ectopy) findings
- Clinical (clinically dx ± sx) vs. subclinical (asx & ID'd by monitor)
- **Paroxysmal** (terminate w/in 7 d), **persistent** (>7 d), **long-standing persistent** (>12 mo), s/p **successful ablation**, or **permanent** (no plan to restore or maintain SR)

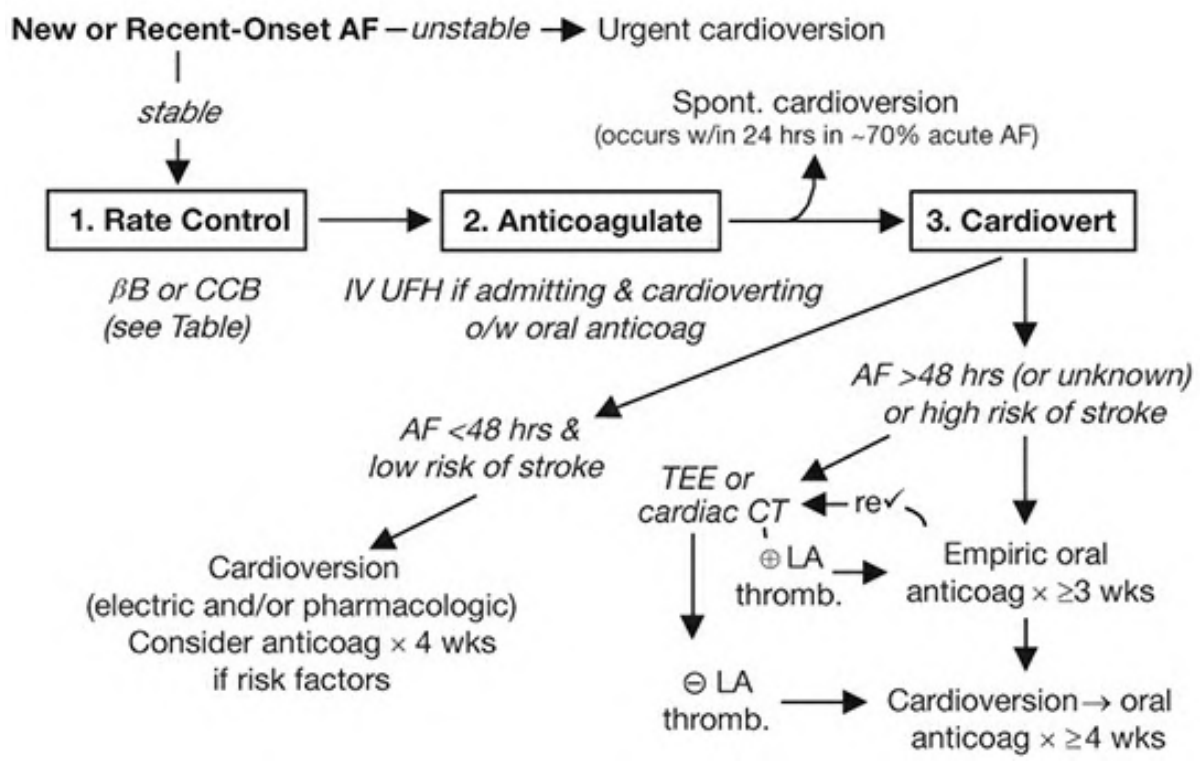
Epidemiology and etiologies (*Circ A&E* 2018;11:e006350)

- 1–2% of pop. has AF (10% of those age ≥80); M > F; lifetime risk ~25%; mean age 75 y
- Risk factors: age, HTN, ischemia, valve dis., CMP, DM, hyperthyroid, obesity, OSA, EtOH
- Acute (up to 50% w/o identifiable cause)
  - **Cardiac:** HF, new CMP, myo/pericarditis, ischemia/MI, HTN crisis, valve dis., cardiac surg
  - **Pulmonary:** acute pulmonary disease or hypoxemia (eg, COPD flare, PNA), PE, OSA
  - **Metabolic:** high catecholamine states (stress, infection, post-op, pheo), thyrotoxicosis
  - **Drugs:** alcohol, cocaine, amphetamines, ibrutinib
  - **Neurogenic:** subarachnoid hemorrhage, ischemic stroke
- Aggressive mgmt of HTN, OSA, & EtOH (*NEJM* 2020;382:20) to ↓ risk

Evaluation

- H&P, ECG, CXR, TTE (LA size, thrombus, valves, LV fxn, pericardium), BMP, TFTs
- Sleep study if suspect OSA; r/o MI not necessary unless other ischemic sx
- In acute AF <48º, ~70% spont. convert to SR w/in 48 hrs (*NEJM* 2019;380:1499)

Figure 1-4 Approach to acute AF



Rate Control (if sx, goal HR <80; if asx & EF >40%, goal HR <110; *Circ* 2024;149:e61)				
	Agent	**Acute (IV)**	**Maint. (PO)**	**Comments**
CCB	**Verapamil**	5–10 mg over 2′ may repeat in 30′ 5 mg/h infusion	180–480 mg/d (ER)	↓ BP. Can worsen HF, avoid if EF <40%. Preferred if severe COPD. Can ↑ dig levels.
	Diltiazem	0.25-0.35 mg/kg over 2′; may repeat in 15′; 5–15 mg/h infusion	120–360 mg/d (ER)	
βB	**Metoprolol**	2.5–5 mg over 2′ may repeat q5′ × 3	50–400 mg/d (ER)	↓ BP. Preferred if CAD. Risks: HF & bronchospas.
Digoxin (onset >30 min)		0.25 mg q2h up to 1.5 mg	0.0625–0.25 mg qd (adj for CrCl)	Consider in HF or low BP Poor exertional HR ctrl
Amiodarone		300 mg over 1 h → 0.5–1 mg/min × 24 h	100–200 mg QD	Consider in HF or low BP Long-term potential tox

IV βB, CCB, and digoxin ***contraindicated*** if evidence of WPW (ie, pre-excitation or WCT) since may facilitate conduction down accessory pathway leading to VF; ∴ use procainamide, ibutilide, or DCCV

Cardioversion

- Consider if: 1st AF, sx, tachycardia-mediated CMP, or difficult to rate control
  - If AF >48 h 2–5% risk of stroke w/ cardioversion (*pharmacologic or electric*); ∴ either TEE or cardiac CT to r/o thrombus or ensure therapeutic anticoag ≥3 wk prior
  - If needs to cardiovert urgently, anticoagulate acutely (eg, IV UFH) and for ≥4 wks after
- In stable Pts, recent-onset (<36 h), sx AF, no Δ in % in SR at 4 wks w/ early cardioversion vs. wait & see (βB + a/c) (69% spont., 28% req cardioversion) (*NEJM* 2019;380:1499)
- Likelihood of success ∝ AF duration & atrial size; control precipitants (eg, vol status)
- Before electrical cardiovert, consider pre-Rx w/ AAD (eg, amio), esp. if 1st cardiovert failed
- For pharmacologic cardioversion, class III (eg, ibutilide) & IC AAD have best efficacy
- If SR returns (spont. or w/ Rx), atria may be *mech. stunned*; also, high risk of recurrent AF over next 3 mo. **∴ Anticoag postcardioversion ≥4 wk.**

Rhythm control (*JACC* 2022;79:1932; *EHJ* 2021;42:373; *Circ* 2024;149:e1; *JAMA* 2025;333:329)

- Increasingly preferred; especially if sx and/or with low LVEF
- For recent AF (up to 1 yr, most w/in ~1 mo), rhythm control w/ AAD (IC, III) and/or ablation (if persists) superior to usual care for achieving SR and ↓ MACE (*NEJM* 2020;383:1305)

Antiarrhythmic Drugs (AAD) for AF (*EHJ* 2024;45:3357; *Circ* 2024;149:e80)				
	Agent	**Conversion**	**Maintenance**	**Comments**
III	Amiodarone	5–7 mg/kg IV over 30–60′ → 1 mg/min, 6–10 g load	200–400 mg qd (most effective AAD for SR)	↑ QT, TdP rare. Often delay to convert. Poss. pulm, liver, thyroid tox. ↑ INR w/ warfarin.
	Dronedarone	n/a	400 mg bid	↓ side effects & effic. vs. amio Contraindicated in HF
	Ibutilide	1 mg IV over 10′ may repeat × 1	n/a	Contraindic. if ↓ K or ↑ QT (2–7% risk of TdP): give w/ IV Mg; avoid if EF ≤40% (↑ TdP)
	Dofetilide	500 µg PO bid	500 µg bid	↑ QT, ↑ risk of TdP; renal adj
	Sotalol	n/a	80–160 mg bid	✓ for ↓ HR, ↑ QT; renal adj
IC	Flecainide	300 mg PO × 1	50–150 mg bid	PreRx w/ AVN blocker. Ø *if structural/ischemic heart dis.*
	Propafenone	600 mg PO × 1	150–300 mg tid	
IA	Procainamide	1 g IV over 30′	n/a	↓ BP; ↑ QT; AV block
Underlying disease & maintenance AAD of choice: *None* or minimal (incl HTN w/o LVH): class IC ("pill in pocket"), dofetilide, dronedarone, amio ***HTN w/ LVH:*** amio; ***CAD:*** sotalol, dofetilide, amio, dronedarone; ***HF***: amio, dofetilide				

Ablation (*Circ* 2024;149:e84)

- Controlling triggers in pulm vv effective when little atrial fibrosis; as AF persists, harder
- Pulm vein isolation (radiofreq, cryo, or pulsed field) has 50–70% success and superior to AAD (*NEJM* 2016;374:2235; 2021;384:305 & 316; 2023;389:1660; 2025;392:1497)
- ↓ sx burden, ↑ QoL, & ↓ progression to persistent (*NEJM* 2023;388:105; *JAMA* 2024;332:1165)
- Adjunct to AAD to maintain rhythm control and ↓ CV complications (*NEJM* 2020;383:1305)
- If NYHA II–IV + EF <35%, ablation ↓ D/HF hosp vs. rate/rhythm meds (*NEJM* 2018;378:417)
- In end-stage HF Pts referred for txp, ↓ death, LVAD, or urgent txp (*NEJM* 2023;389:1380)
- In HF patients across spectrum of EF, ablation appears to ↓ death (*Circ* 2021;143:1377)
- No need to interrupt a/c (and cont. ≥3 mos afterward and long term if CHA_2DS_2-VASc ≥2)
- Rare complications (<1%): stroke, tamponade, phrenic nerve injury, PV stenosis, esophageal-LA/mediastinal fistula

Oral anticoagulation (*EHJ* 2024;45:3314; *Circ* 2024;149:e1)

- Stroke risk ~4.5%/y but varies; a/c → 68% ↓ stroke but ↑ bleeding
- **CHA_2DS_2-VASc** to guide Rx: **C**HF (1 point); **H**TN (1); **A**ge ≥75 y (2); **D**M (1), **S**troke/TIA (2); **V**ascular disease (eg, MI, PAD, Ao plaque) (1); **A**ge 65–74 (1); ♀ **S**ex **c**ategory (1)
- **Score ≥2 in ♂ or ≥3 in ♀ → anticoagulate;** scores 1 in ♂ or 2 in ♀ → **consider anticoag** or ASA or no Rx; **score 0 for men or 1 for women** → reasonable to not Rx
- *A/c regardless of CHA_2DS_2-VASc:* mod-to-sev rheumatic MS, mec valve, HCM, ? amyloid
- **Rx options: DOAC** (NVAF only) preferred over warfarin (INR 2–3)
- AF + CAD/PCI: consider DOAC + clopi (not ticag or prasugrel) + ASA (d/c ~1–4 wks) (*Circ* 2021;143:583); consider DOAC only after 12 mos (*NEJM* 2024;391:2075)

Nonpharmacologic stroke prevent (*Heart Rhythm* 2023;20:e1; *JACC* 2022;79:1)

- If contraindic. to long-term OAC, consider perc. left atrial appendage (LAA) occlusion. Postproc: OAC + ASA × 45 d → DAPT x 4.5 mos or just DAPT x 6 mos. Then ASA lifelong.

- Consider after ablation: similar thrombotic risk & less bleeding (*NEJM* 2025;392:1277)
- Consider surgical LAA occlusion if undergoing cardiac surgery (*NEJM* 2021;384:2081)

Atrial flutter

- Macroreentrant atrial loop. Typical involves cavotricuspid isthmus (if counterclockwise, flutter waves ⊖ in inf leads, if clockwise, ⊕). Atypical: other pathways related to prior scar.
- Risk of stroke similar to that of AF, ∴ anticoagulate same as would for AF
- Ablation of typical (cavotricuspid isthmus) AFL has 95% success rate

Subclinical AF

- If lasts ≥24 hrs and CHA_2DS_2-VASc ≥2, reasonable to anticoagulate (*Circ* 2024;149:e40)
- If 6 min–24 hrs, may be reasonable to a/c, especially if prior stroke or TIA (*NEJM* 2023;389:1167 & 2024;390:107; *Circ* 2024;149:981; *Lancet Neurol* 2025;24:140)

SYNCOPE

Definition

- Symptom of sudden transient loss of consciousness due to global cerebral hypoperfusion
- If CPR or cardioversion required, then SCD and not syncope (different prognosis)
- Presyncope = prodrome of light-headedness without LOC

Etiologies (*JACC* 2017;70:e39; *EHJ* 2018;39:1883)

- **Vasovagal** (aka neurocardiogenic, ~25%): ↑ sympathetic tone → vigorous contraction of LV → LV mechanoreceptors trigger ↑ vagal tone (hyperactive Bezold–Jarisch reflex) → ↓ HR (cardioinhib.) and/or ↓ BP (vasodepressor). Cough, deglutition, defecation, & micturition → ↑ vagal tone and thus can be precipitants. Carotid sinus hypersensitivity (exag vagal resp to carotid massage) is related disorder.
- **Orthostatic hypotension** (~10%)
  - hypovolemia/diuretics, deconditioning; vasodilat. (esp. if combined w/ ⊖ chronotropes)
  - autonomic neuropathy [1° = Parkinson's, MSA/Shy–Drager, Lewy body dementia, POTS (dysautonomia in the young); 2° = DM, EtOH, amyloidosis, CKD] (*JACC* 2018;72:1294)
- **Cardiovascular** (~20%, more likely in men than women)
  - *Arrhythmia* (~15%): challenging to dx because often transient
    - Bradyarrhythmias: SB, SSS, high-grade AV block, ⊖ chronotropes, PPM malfunction
    - Tachyarrhythmias: VT, SVT (syncope rare unless structural heart disease or WPW)
  - *Mechanical* (~5%)
    - Endocardial/Valvular: critical AS, MS, PS, prosthetic valve thrombosis, myxoma
    - Myocardial: outflow obstruction from HCMP (or VT); pericardial: tamponade
    - Vascular: PE (in ~25% w/o alt dx; *NEJM* 2016;375:1524), PHT, AoD, ruptured AAA
- **Neurologic** (~10%): vertebrobasil insuff, cerebrovasc dissection, SAH, TIA/CVA
- Misc. causes of LOC (but not syncope): seizure, ↓ glc, hypoxia, narcolepsy, psychogenic

Workup (etiology cannot be determined in ~40% of cases) (*JAMA* 2019;321:2448)

- *H&P incl. orthostatic VS have highest yield and most cost-effective*
- *R/o life-threatening dx including: cardiac syncope, severe blood loss, PE, SAH*
- **History** (from Pt and *witnesses* if available)
  - activity and posture before the incident
  - precipitating factors: exertion (AS, HCMP, PHT), positional Δ (orthostatic HoTN), stressors

such as sight of blood, pain, emotional distress, fatigue, prolonged standing, warm environment, N/V, cough/deglutition/micturition/defecation (neurocardiogenic), head turning or shaving (carotid sinus hypersens.); arm exercise (subclavian steal)
sudden onset → cardiac; prodrome (eg, diaphoresis, nausea, blurry vision) → vasovagal
associated sx: chest pain, palp., neurologic, postictal, bowel/bladder incontinence (convulsive activity for <10 sec may occur w/ transient cerebral HoTN & mimic seizure)

- **PMH:** prior syncope, previous cardiac or neuro dis.; cardiac more likely if >35 y, known structural heart dis., h/o AF, CV prodrome, syncope while supine or exertional, cyanosis
- **Medications that may act as precipitants**
  vasodilators: α-blockers, nitrates, ACEI/ARB, CCB, hydralazine, phenothiazines, antidep.
  diuretics; ⊖ chronotropes (eg, βB and CCB)
  proarrhythmic or QT prolonging: class IA, IC, or III antiarrhythmics (see "ECG")
  psychoactive drugs: antipsychotics, TCA, barbiturates, benzodiazepines, EtOH
- **Family history:** CMP, SCD, syncope (vasovagal may have genetic component)
- **Physical exam**
  VS incl. *orthostatics* (⊕ if supine → standing results in ≥20 mmHg ↓ SBP or ≥10 ↓ DBP or SBP <90 mmHg w/in 3 min; POTS if ≥30 bpm ↑ HR w/in 10 min), BP in both arms
  Cardiac: HF (↑ JVP, displ. PMI, S_3), murmurs, LVH (S_4, LV heave), PHT (RV heave, ↑ P_2)
  Vascular: ✓ for *asymmetric pulses*, carotid/vert/subclavian *bruits; carotid sinus massage* to ✓ for carotid hypersens (if no bruits): ⊕ if asystole >3 sec or ↓ SBP >50 mmHg
  Neurologic exam: focal findings, evidence of tongue biting, micturition
- **ECG** (abnormal in ~50%, but only definitively identifies cause of syncope in <10%)
  Conduction: SB <40 bpm, sinus pauses >3 sec or sinus arrhythmia, AVB, BBB/IVCD
  Arrhythmia: ectopy, ↑ or ↓ QT, pre-excitation (WPW), Brugada, ε wave (ACM), SVT/VT
  Ischemic changes (new or old): atrial or ventricular hypertrophy
- Lab: glc, Hb, HCG (pre-menop ♀), ? D-dimer, ? troponin/NT-proBNP (↓ yield w/o other s/s)

Other diagnostic studies (consider based on results of H&P and ECG)

- Ambulatory ECG monitoring if suspect arrhythmogenic syncope (vide infra)
- Echo: consider to r/o structural heart disease (eg, CMP [incl HCMP & ACM], valvular disease [incl AS, MS, MVP], myxoma, amyloid, PHT, ± anomalous coronaries)
- Tilt table: debated utility due to poor Se/Sp/reproducibility; consider if suspected neuro-cardiogenic, orthostatic HoTN, POTS, or psychogenic, and initial eval unrevealing

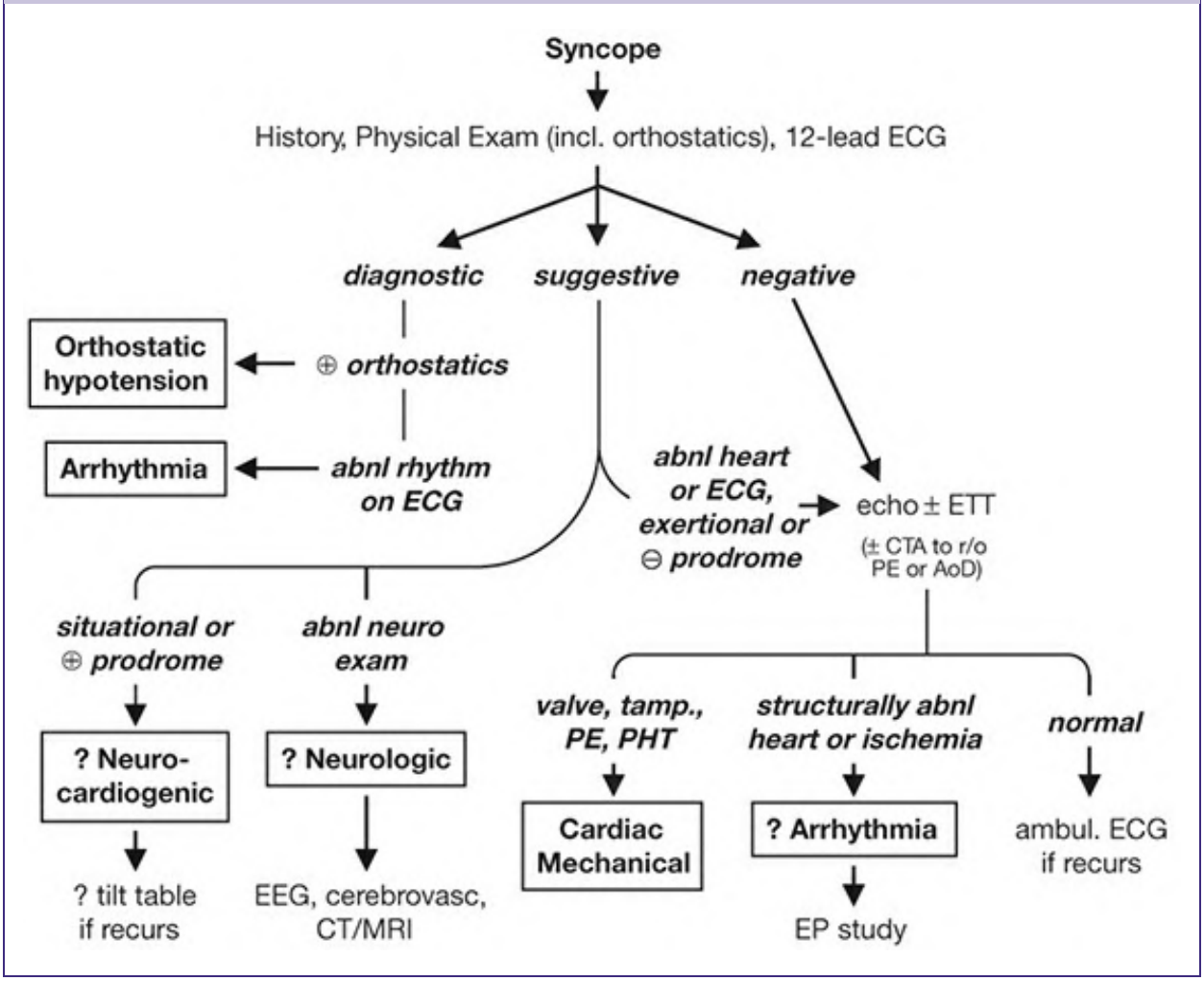
Cardiac Rhythm Monitors (*Circ* 2017;136:e60)

Type	Description	Optimal Patient
Holter	Continuous recording for 24–72 hrs, some models up to 2 wks. Sx correlation with Pt diary or annotations.	Frequent sx. Sx + arrhythmia in 4%; asx + arrhythmia in 13%; sx but no arrhythmia in 17%.
Event monitor	Activated by Pt to record rhythm; can transmit to MD via analog phone	Limited utility in frank syncope unless established prodrome
Ext. loop recorder	Continuously records rhythm for 1–2 wks, ∴ can be activated *after* an event	Frequent spontaneous sx, likely to occur w/in 2 wks
Mobile telemetry	Records & transmits data (up to 30 d) w/ sensed arrhythmia or Pt activation	High-risk Pts in whom real-time feedback potentially useful
Implantable cardiac monitor	SC-implanted device, battery life 2–3 y. Triggered by Pt or bystander to store event. Transtelephonic transmission.	Recurrent infrequent syncope (<1/mo). Estab dx more than conventional testing.

- ETT/CCTA/cath: esp. w/ exertional syncope; r/o ischemia or catechol-induced arrhythmia
  50% abnl (inducible VT, conduction abnormalities) if heart disease

- Electrophysiologic studies (EPS): consider in high-risk Pts in whom tachy or brady etiology is strongly suspected (eg, prior MI), but cannot be confirmed; avoid if ECG/Echo normal
- Cardiac MRI: helps to dx sarcoid or ACM if suggestive ECG, echo (eg, RV dysfxn) or ⊕ FHx
- Neurologic studies (cerebrovascular studies, CT, MRI, EEG): if H&P suggestive; low yield

Figure 1-5 Approach to syncope (adapted from *JACC* 2017;70:e39)



High-risk features (admit w/ tele; *CMAJ* 2016;188:e289; *JACC* 2017;70:620; *EHJ* 2018;39:1883)

- Age >60 y, h/o CAD, HF/CMP, valvular or congenital heart dis., arrhythmias, FHx SCD
- Syncope c/w cardiac cause (⊖ prodrome, exertional, supine, trauma) or recurrent
- Complaint of chest pain or dyspnea; abnl VS, cardiac, pulm, or neuro exam; low Hct
- ECG suggesting conduction abnormality, arrhythmia, or ischemia; Pt w/ PPM/ICD
- Canadian Syncope Risk Score: low risk & no arrhythmia in ED × 2 h, 0.2% risk over 30 d

Treatment (*JACC* 2017;70:620 & 2019;74:2410; *EHJ* 2018;39:1883)

- Arrhythmia, cardiac mechanical or neurologic syncope: treat underlying disorder, ? ICD if Brugada pattern, sarcoid, ACM/ARVC, early repol + syncope
- Vasovagal: avoidance of triggers; physical counterpressure; consider ↑ Na & fluid intake, fludrocortisone or midodrine (*JACC* 2016;68:1; *Ann Intern Med* 2021;174:1349); SSRI; ? βB; consider PPM if recurrent + pauses on recorder or tilt test (*EHJ* 2021;42:508)
- Orthostatic: 2–3 L fluid & 10 g Na per day; rise from supine to standing *slowly*, compression

stockings; consider: midodrine, fludrocortisone, droxidopa, ? pyridostigmine, ? octreotide

Prognosis (*Ann Emerg Med* 1997;29:459; *NEJM* 2002;347:878)

- 22% overall recurrence rate if idiopathic, else 3% recurrence
- Cardiac syncope has poor prognosis (20–40% 1-y SCD rate); vasovagal good prognosis
- ✓ state driving laws and MD reporting requirements. Consider appropriateness of Pt involvement in exercise/sport, operating machinery, high-risk occupation (eg, pilot).

CARDIAC RHYTHM MANAGEMENT DEVICES

Pacemaker Code				
A, atrial; V, vent; O, none; I, inhibition; D, dual; R, rate-adaptive	**1st letter**	**2nd letter**	**3rd letter**	**4th letter**
	Chamber paced	Chamber sensed	Response to sensed beat	Program features

Common Pacing Modes	
VVI	Ventricular pacing on demand w/ single lead in RV. Sensed ventricular beat inhibits V pacing. Used in chronic AF with symptomatic bradycardia.
DDD	A & V sensing/pacing (RA & RV leads). Native A beat inhib A pacing & *triggers V pacing* → tracking of intrinsic atrial activity. Maintains AV synchrony, ↓ AF.
Mode Switch	In atrial tachyarrhythmia (eg, AF), PPM Δs from DDD to nontracking mode (eg, VVI). Prevents PPM from pacing at max V rate in response to rapid atrial rate.
Magnet over gen.	PPM: fixed rate pacing (VOO/DOO). ICD: no shock, pacing preserved. Indic: ✓ capture; surgery; inapprop PPM inhib/ICD shock, PM-mediated tachy
Leadless intracardiac PPM for RV or AV synchronous pacing (*JACC Clin EP* 2020;6:94). His or L bundle pacing: more physiologic than RV pacing or even CRT (*JACC* 2018;72:927).	

Indications for Permanent Pacing (*Circ* 2017;136:e60 & 2018;140:e333)	
AV block	2° type II, high-grade or 3° AVB; sx marked 1° or 2° type I AVB or asx with Lamin A/C or neuromuscular disease; bifasc or alter. L & RBBB
Sinus node	Sx sinus node dynfxn; reasonable if tachy-brady w/ sx brady
Tachy-arrhythmia	AF w/ SSS iso rate-controlling drugs; sustained pause-dependent VT; ? high-risk congenital long QT
Syncope	Carotid sinus hypersens. w/ asystole >3 sec or AVB. Syncope w/ LBBB and HV >70 ms on EPS. ? Recurrent vasovagal syncope w/ prolonged pauses.

Pacemaker Complications		
Issue	**Manifestation**	**Description & Etiologies**
Perforation	Effusion/tamp/pain	Typically acute, consider if HoTN
Fail to pace	Brady w/o pacing	Oversense → inapprop. inhib; battery depletion

Fail to capture	Pacing w/o P or QRS	Lead fx/dislodgment; local tissue rxn; abnl lytes
Fail to sense	Inapprop. pacing	Lead dislodgment or sensing threshold too high
PM-mediated tachycardia	WCT at device upper rate	Seen w/ DDD. V → A retrograde conduction; sensed by A lead → triggers V pacing → etc.
PM syndrome	Palpit, HF	Seen w/ VVI, due to loss of AV synchrony

Cardiac resynch therapy (CRT) (*Heart Rhythm* 2023;20:e17)

- 3-lead pacemaker: RA, RV, coronary sinus; for CS lead, R>S in V_1, ⊖ in I and aVL
- Synch LV fxn (↑ CO/EF, ↓ adv remodeling); ↓ HF sx & hosp, ↑ survival (*NEJM* 2010;363:2385)
- **Indications:** LVEF ≤35% + HF despite med Rx + SR + LBBB ≥150 ms. No clear evidence of benefit if QRS <150 ms or RBBB (*Circ* 2023;147:812); consider in Pts w/ LVEF 36–50% with indication for PPM and anticipated high pacing burden (*NEJM* 2013;368:1585).

Implantable cardiac defibrillator (ICD) (*Circ* 2017;138:e272)

- RV lead: defib & pacing (± antitachycardia pacing [ATP] = burst pacing > VT rate to stop VT); ± RA lead for dual-chamber PPM. Subcut-ICD (consider if young), but Ø pace/ATP.
- **2° prev**: survivors of VT/VF arrest w/o revers cause; asx sustained VT + struct. heart dis.
- **1° prev**: IHD (wait ideally ≥40 d after MI; 90 d after revasc): LVEF ≤30% *or* ≤35% & NYHA II–III *or* ≤40%, spont NSVT & inducible.
  NICM (wait ≥90 d after starting GDMT): LVEF ≤35% & NYHA II–III.
  More recently, for niCMP ICD ↓ SCD but not overall mortality (*NEJM* 2016;375:1221).
  High-risk CMP (w/o meeting above criteria): HCM, ACM, sarcoid, laminopathy, Chagas.
  Channelopathies: LQTS or Brugada if syncope or high-risk. ACHD: if SCD risk factors.
  Life expectancy must be >1 *y.*
- Wearable vest as bridge while waiting for ICD, but no benefit in RCT (*NEJM* 2018;379:1205)
- Subcutaneous ICD noninferior in patients without PPM indication (*NEJM* 2020;383:526). SC ICD coupled w/ leadless PPM being explored (*NEJM* 2024;391:1402).
- **Risks:** inapprop shock in ~15–20% at 3 y (commonly d/t misclassified SVT); infxn; lead fx
- ICD discharge: ✓ device to see if approp; r/o ischemia; 6-mo driving ban (✓ state law)
- MRI: new devices OK; older may be OK (*NEJM* 2017;377:2555). Consult prescan.

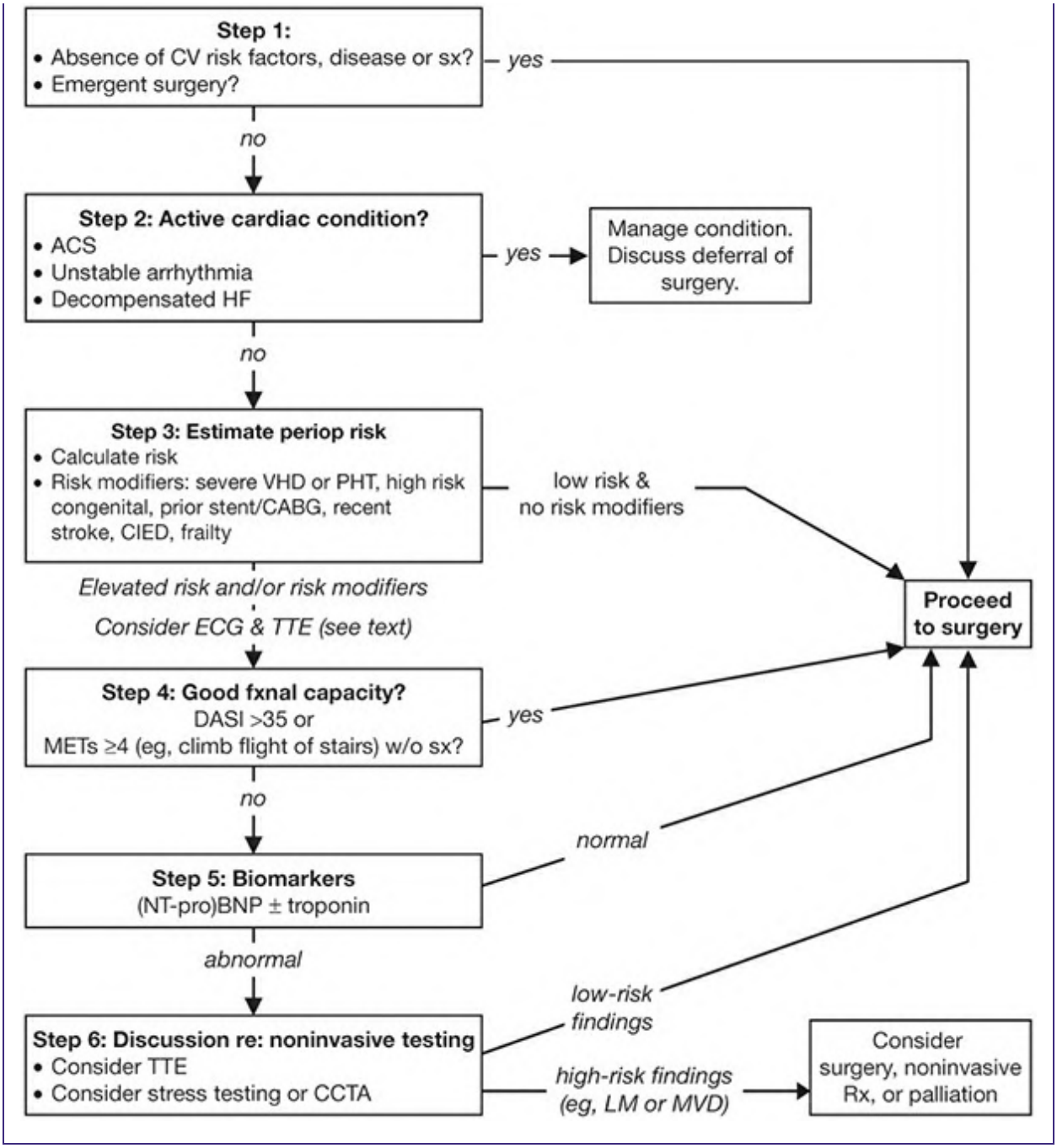
Device infection (*Heart Rhythm* 2017;14:e503, *NEJM* 2019;380:1895)

- Presents as *pocket infection* (warmth, erythema, tenderness) and/or *sepsis w/ bacteremia*
- ~2% over 5 y; if *S. aureus* bacteremia, infxn in ≥35%; antibacterial envelope ↓ risk
- TTE/TEE used to help visualize complic. (eg, vegetation), but even ⊖ TEE does not r/o
- Rx: abx; system removal if pocket infxn or GPC bacteremia; Ø routine abx prior to inv. proc.

CARDIAC RISK ASSESSMENT FOR NONCARDIAC SURGERY

Preoperative evaluation (*Circ* 2024;150:e351)

Figure 1-6 Approach to pre-op CV eval for non-CV surgery



Preoperative evaluation and testing

- Calculate peri-op CV risk (eg, w/ RCRI, ACS NSQIP, MICA). In general, take into account: prevalent ASCVD & HF; comorbidities (DM, COPD, CKD); surgical risk (high: thoracic & suprainguinal vascular; intermediate: GI, GU, ortho; low: endo, breast, gyn).
- Assess fxnal capacity (eg, DASI) & frailty (≥65 y or <64 y w/ perceived frailty)
- ECG: reasonable if ASCVD, signif arrhythmia, or ischemic sx + planned ↑ risk surgery
- (NT-pro)BNP ± troponin: if ↑ risk surgery & known CV disease, ≥65 y, or ≥45 y w/ CV sx
- TTE: if new dyspnea or sx of HF, suspected Δ LVEF, hx of HF with Δ in sx, suspected ≥ moderate valvular heart disease
- Stress testing or CCTA: consider if ↑ calculated risk and poor or unknown functional capacity (eg,

<4 METs) and ↑ risk surgery; routine coronary angio not recommended
- Revasc prior to elective surgery only in ACS or signif LM disease

Heart failure

- Decomp HF should be optimized prior to surgery & GDMT continued (except SGLT2i)
- For HCM, avoid triggers for LVOT obstruction (tachycardia, reduced preload, etc.)

Valvular heart disease (VHD)

- If significant VHD (eg, severe AS, severe MS, significant regurg), evaluate need for intervention prior to elective surgery (postpone surgery if necessary)
- If severe VHD & surgery urgent, peri-op hemodynamic monitoring may be reasonable (eg, AS: ↑ risk even if asx; maintain preload, avoid hypotension, watch for AF)

Pulmonary hypertension

- Continue pulmonary vasodilators
- For ↑ risk surgery, consider invasive hemodynamics and short-term inh pulm vasodilators

Cardiac implantable electronic devices

- Consider likelihood & conseq. of electromagnetic interference; reprogram/magnet as needed

Pre- & perioperative pharmacologic management (*Circ* 2024;150:e351)

- **ASA:** continue in Pts w/ existing indication
- **DAPT:** Continue & delay elective surg until (ideally) ≥1 mo after BMS and ≥3–6 mos after DES. If cannot, and high-risk stent, cont. ASA & consider bridging w/ cangrelor.
- **Oral anticoagulant**: except for low proc. bleeding risk, hold DOAC ≥2 d pre-op and ≥3 d if renal impairment (≥4 d if dabigatran); hold VKA ≥5 d. If high thrombotic risk (eg, mech MV, recent VTE, or cardioembolic stroke), consider bridge VKA w/ UFH.
- β**B:** continue if on chronically. Do not stop abruptly post-op (may cause reflex symp. activation); use IV if unable to take PO. Reasonable to initiate if new indication prior to surgery, but do so ≥1 wk prior to surgery and use low-dose, short-acting βB.
- **ACEI/ARB/ARNi** holding for 24 h pre-op may ↓ intraop HoTN, but does not change clinical outcomes. Reasonable to continue, especially in HFrEF (*JAMA* 2024;332:970).
- **Statins:** ↓ ischemia & CV events in Pts undergoing vascular surg (*NEJM* 2009;361:980)
- **SGLT2i**: hold for 3–4 d prior to elective surgery to prevent euglycemic DKA
- **GLP-1RA**: can continue, but consider liquid diet for 24 hrs prior given risk for gastroparesis

Atrial fibrillation

- Rate control with BB or CCB; digoxin as adjunct or if former contraindicated
- If refractory to rate control, consider AAD and/or cardioversion
- If new-onset AF, anticoag based on CHADS-VASc; outPt surveillance for AF burden and thromboembolic risk stratification

PERIPHERAL ARTERY DISEASE (PAD)

Clinical features (*NEJM* 2016;374:861; *Circ* 2024;149:e1313)

- Risk factors: age (esp >65 y), **smoking**, **DM**, HTN, HLD, CKD, FHx PAD
- **Asymptomatic PAD**: may have ↓ functional capacity

- **Chronic symptomatic: claudication** = ache/cramp, often in calves, buttocks, or thighs, precip by walking & relieved by stopping (vs. spinal stenosis, qv); Leriche syndrome (aortoiliac disease) = claudication, ↓ or Ø fem pulses, & erectile dysfxn
- **Chronic limb-threatening ischemia (CLTI): rest pain** (↑ w/ elevation b/c ↓ perfusion), **ulcer** (typically at pressure foci, often dry; in contrast, venous ulcers are more often at medial malleolus, wet, and with hemosiderin deposition) or **gangrene**, and >2-wk duration (implies chronicity vs. acute limb ischemia; vide infra)

Diagnosis

- ↓ peripheral pulses ± femoral bruits; chronic signs: wounds, hair loss, skin atrophy
- Ankle brachial index (ABI) at rest: nl 1–1.4; borderline 0.91–0.99; abnl ≤0.90; if >1.4, non-dx possibly due to calcified noncompressible vessel → ✓ PVR, TBI (toe-brachial index). If ABI abnl → segmental ABI w/ PVR to localize disease. If ⊕ sx but nl/borderline ABI, ✓ exercise ABI (↓ lower extrem BP after exercise: ≥20% ↓ in ABI or ≥30 mmHg ↓ at ankle).
- Duplex arterial U/S; CTA w/ distal run-off; MRA or angio if ? dx or ? intervention

Treatment (chronic) (*JACC* 2024;84:936)

- Risk factor modification incl. quit smoking & aggressive LDL-C reduction (<55 mg/dL)
- Supervised exercise to ↑ fxnal status & QoL (*JAMA* 2021;325:1266 & 2022;327:1324)
- Cilostazol (contraindic. if HF) improves sx; specialized foot care/wound management
- If DM, GLP-1RA ↑ walking dist., ABI, & QoL and ↓ rescue Rx or death (*Lancet* 2025;405;1580)
- SAPT (ASA or clopi). Adding riva 2.5 mg bid to ASA ↓ MALE & MACE (*Lancet* 2018;391:219) & ↑ bleeding. Also data for DAPT w/ ASA + ticag (*JACC* 2016;67:2719 & *NEJM* 2019;381:1309).
- Endovascular (angioplasty vs. stent) or surgical revasc if limiting/refractory sx after initiating GDMT (↑ QoL, walking) & in all CLTI if feasible (preserve limb) (*NEJM* 2023;387:2305)
- Post-revasc: riva 2.5 mg bid + ASA (*NEJM* 2020;382:1994); if contraindic., DAPT reasonable

Acute limb ischemia (ALI)

- Sudden decrement in limb perfusion (ie, acutely cold & painful) that threatens viability
- Etiologies: embolism > acute thrombosis (eg, athero, APS, HITT), trauma to artery
- Clinical manifestations (**6 Ps**): pain (distal to proximal, ↑ in severity), poikilothermia, pallor, pulselessness, paresthesias, paralysis
- Testing: pulse & neuro exam; arterial & venous Doppler; angiography, ± CTA or MRA
- Emergent consult w/ vascular med/surgery for revasc; immediate UFH ± intra-arterial lytic

Categorization & Treatment of ALI

Audible Doppler		Motor Fxn Loss	Sen. Loss	Cap. Refill	Status	Treatment
Art.	Ven.					
Y	Y	None	None	OK	Viable	A/C + urgent revasc
N	Y	Some	Some	Slow	Threatened	A/C + *emerg* revasc
N	N	Total	Complete	Absent	Irreversible	Amputation

DYSPNEA

Pathophysiology	Etiologies
Airway obstruction (↑ resistance to airflow)	**Asthma, COPD**, bronchiectasis, cystic fibrosis, tumor, foreign body, vocal cord dysfunction, anaphylaxis
Alveolar/parenchymal disease	**Pulmonary edema**: *cardiogenic or noncardiogenic* **ILD; pneumonia**; atelectasis
Vascular (V/Q mismatch)	Large vessel: **PE**, tumor emboli Small vessel: PHT, vasculitis, ILD, emphysema, PNA
Chest wall (↑ resistance to expansion; weakness of respir. muscles)	Pleural disease**: large effusion**, fibrosis, pneumothorax Chest wall/diaphragm: kyphoscoliosis, ↑ abd girth Neuromuscular disorders (ALS, GBS, MG) Hyperinflation (COPD, asthma)
Stimulation of receptors	Chemoreceptors: **hypoxemia**, metabolic acidosis Mechanoreceptors: ILD, pulmonary edema, PHT, PE
↓ **O_2 carrying cap.** (but nl P_aO_2)	**Anemia**, methemoglobinemia, CO poisoning
Psychological	Anxiety, panic attack, depression, somatization

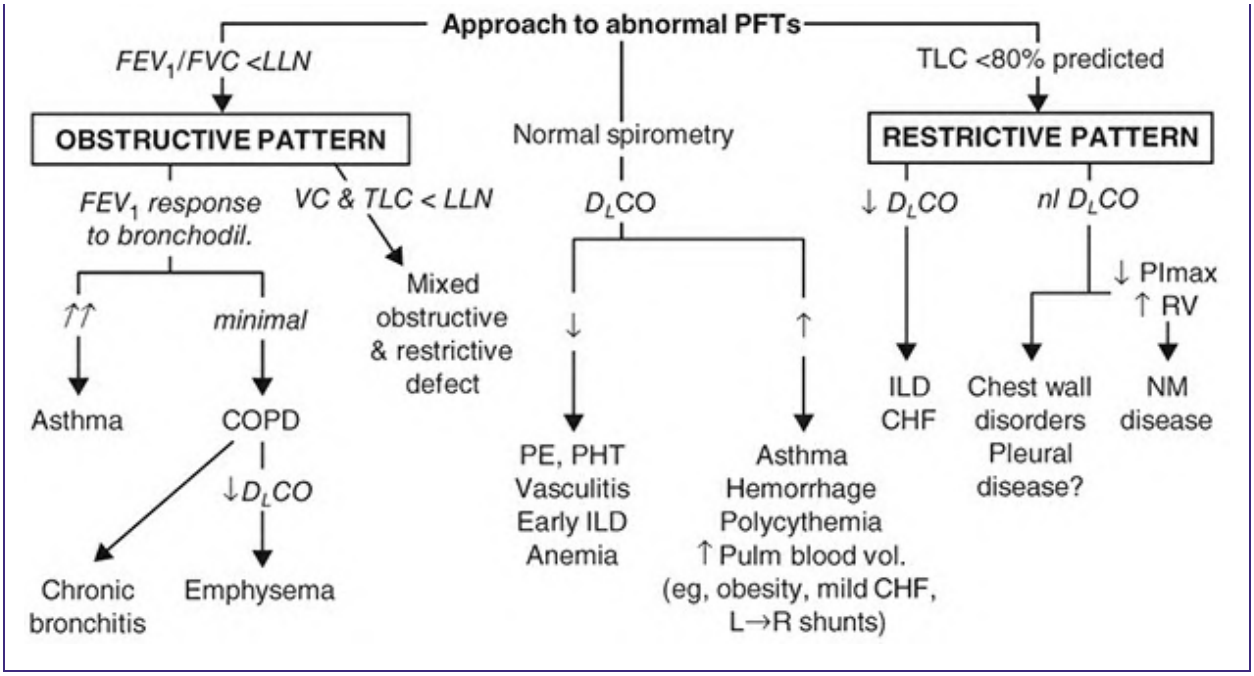
Evaluation

- History: quality of sensation, tempo, positional dependence, exac./allev. factors, exertion
- Cardiopulmonary exam, S_aO_2, CXR (see Appendix & Radiology inserts), ECG, ABG, U/S
  Predictors of CHF: h/o CHF, PND, S_3, CXR w/ venous congestion, AF (*JAMA* 2005;294:1944)
  Dyspnea w/ nl CXR: CAD, asthma, PE, PHT, early ILD, anemia, acidosis, NM disease
- Based on results of initial evaluation: PFT, chest CT, TTE, cardiopulmonary testing
- **BNP & NT-proBNP** ↑ in CHF (also ↑ in AF, RV strain from PE, COPD flare, PHT, ARDS)
  BNP <100 pg/mL to r/o CHF (90% Se), >400 to r/i (*NEJM* 2002;347:161)
  NT-proBNP <300 pg/mL to r/o CHF (99% Se); age-related cut points to r/i:
  >450 pg/mL (<50 y), >900 (50–75 y), >1800 (>75 y) (*EHJ* 2006;27:330)
  ↑ in chronic HF, ∴ need to compare to known "dry BNP." May be falsely low in obesity.

PULMONARY FUNCTION TESTS (PFTs)

- **Spirometry:** evaluate for obstructive disease
  Flow-volume loops: diagnose and/or localize obstruction
  Bronchodilator: indicated if obstruction at baseline or asthma clinically suspected
  Methacholine challenge: helps dx asthma if spirometry nl, >20% ↓ FEV_1 → asthma
- **Lung volumes:** evaluate for hyperinflation or restrictive disease including NM causes
- **D_LCO:** evaluates functional surface area for gas exchange; helps differentiate causes of obstructive and restrictive diseases and screens for vascular disease & early ILD

Figure 2-1 Approach to abnormal PFTs



PFT laboratories should adopt a race-neutral approach to PFT interpretation by reporting and interpreting results using race-agnostic reference equations (*AJRCCM* 2023;207:978)

ASTHMA

Definition and epidemiology (*Lancet* 2023;401:858)

- Chronic inflam disorder w/ **airway hyperresponsiveness** + **variable airflow obstruction**
- Affects 5–10% population; ~85% of cases by age 40 y

Clinical manifestations (*NEJM* 2013;369:549)

- Classic triad = **wheezing, cough, dyspnea;** others include chest tightness, sputum; symptoms typically *chronic* with *episodic exacerbation*
- Precipitants **(triggers)**
  respiratory irritants (smoke, perfume, etc.) & *allergens* (pets, dust mites, pollen, etc.)
  infections (URI, bronchitis, sinusitis)
  drugs (eg, ASA & NSAIDs via leukotrienes, bB via bronchospasm, MSO_4 via histamine)
  emotional stress, cold air, exercise (increase in ventilation dries out airways)

Physical examination

- Wheezing and prolonged expiratory phase
- Presence of nasal polyps, rhinitis, rash → *allergic component*
- Exacerbation → ↑ RR, ↑ HR, accessory muscle use, diaphoresis, pulsus paradoxus

Diagnostic studies (*JAMA* 2017;318:279)

- **Spirometry:** ↓ FEV_1, ↓ FEV_1/FVC, coved flow-volume loop; lung volumes: ± ↑ RV & TLC
  ⊕ bronchodilator response (↑ FEV_1 ≥12% & ≥200 mL) strongly suggestive of asthma

methacholine challenge (↓ FEV_1 ≥20%) if PFTs nl: Se >90%

- If suspicion for atopic disease, ✓ skin prick test, serum IgE, blood/sputum eos, fractional exhaled nitric oxide (F_ENO; ≥40 parts/billion suggestive of T2 inflammation)

Ddx ("all that wheezes is not asthma…")

- Hyperventilation & panic attacks
- Upper airway obstruction or inh foreign body; laryngeal/vocal cord dysfxn (eg, 2° to GERD)
- CHF ("cardiac asthma"); COPD; bronchiectasis; ILD (including sarcoidosis); vasculitis; PE

"Asthma plus" syndromes

- Atopy = asthma + allergic rhinitis + atopic dermatitis
- Aspirin-exacerbated respiratory disease (Samter's syndrome) = asthma + ASA sensitivity + nasal polyps (*J Allergy Clin Immunol* 2015;135:676)
- ABPA = asthma + pulmonary infiltrates + hypersensitivity to *Aspergillus* (*Chest* 2009;135:805)
  Dx: ↑ IgE to *Asperg.* & total (>1000), ↑ *Asperg.* IgG levels, ↑ eos, central bronchiectasis
  Rx: steroids ± itra-/voriconazole for refractory cases (*NEJM* 2000;342:756)
- Eosinophilic granulomatosis w/ polyangiitis (EGPA, previously Churg–Strauss) = asthma + eosinophilia + granulomatous vasculitis

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Chronic Management

Principles of treatment

- Education & avoidance of environ. triggers (*Lancet* 2015;386:1075); annual immunizations
- Depending on severity, use combo of "controller" (daily) and "reliever" (prn) inhalers to achieve **complete control** = daily sx ≤2 days per wk, Ø nocturnal sx, reliever med ≤2/wk, nl peak expiratory flow rate or FEV_1
- If partially/uncontrolled, assess inhaler adherence/technique, incl. spacer use
- Step up treatment as needed to gain control, step down as tolerated
- Direct Pts to quadruple dose of ICS to abort exacerbations (*NEJM* 2018;378:902)

"Reliever" medications (used prn to quickly relieve sx)

- Low-dose inhaled **corticosteroids** (ICS) · *long-acting* inh **α_2-agonists** (LABA): superior to ICS or β_2-agonist alone; budesonide–formoterol preferred due to quick onset of formoterol (*NEJM* 2019;380:2020; 2022;386:1505 & 2071; *JAMA* 2025;333:143)
- *Short-acting* inh **α_2-agonists** (SABA): albuterol Rx of choice; should not be used as monotherapy (↑ exacerbations compared to ICS-LABA monotherapy) (*NEJM* 2019;380:2020)
- *Short-acting* inh **muscarinic antag.** (ipratropium) ↑ β_2-agonist delivery → ↑ bronchodilation

"Controller" meds (taken daily to maintain control) (*JAMA* 2020;324:2301)

- **ICS** Rx of choice. Superior to LAMA if sputum w/ ≥2% eos (*NEJM* 2019;380:2009). PO steroids may be needed for severely uncontrolled asthma; avoid if possible b/c of systemic side effects.
- LABA (eg, salmeterol, formoterol) safe & ↓ exacerb. when added to ICS (*NEJM* 2018;378:2497)
- *Long-acting* inh **muscarinic antag.** (LAMA; eg, tiotropium, umeclidinium): may consider if sx despite ICS+LABA (*JAMA* 2018;319:1473)
- **Leukotriene receptor antagonists** (LTRA): some Pts very responsive, esp. ASA-sens and exercise-induced. Warning for serious neuropsychiatric effects, including suicide.

Asthma Stepwise Therapy (Adapted from GINA 2023 Guidelines)					
	Step 1	**Step 2**	**Step 3**	**Step 4**	**Step 5**
Sx	<2×/mo	<4–5 d/wk	Daily or noct. sx >1/wk	Step 3 + *low lung fxn*	Uncontrolled on Step 4 Rx
Controller	Low-dose ICS-LABA prn		Low-dose ICS-LABA	Med-dose ICS-LABA	Med- or high-dose ICS-LABA + LAMA ± biologic
Reliever	Low-dose ICS-LABA prn				
Alt. controller	SABA prn coupled w/ ICS prn	Low-dose ICS	Low-dose ICS-LABA	Med- or high-dose ICS-LABA	Med- or high-dose ICS-LABA + LAMA ± biologic
Alt. reliever	SABA prn or ICS-SABA prn				

Formoterol preferred LABA over salmeterol due to having both quick onset and long duration

Immunotherapies/Biologics (*NEJM* 2022;386:157)

- Anti-IL-4Rα (**dupilumab**) blocks IL-4 & IL-13; ↓ exacerb in sev. asthma, ↓ steroid use, ↑ FEV_1 (*NEJM* 2018;378:2475 & 2486)
- Anti-IL-5 (**mepolizumab**, reslizumab) ↓ exacerb in sev. asthma (*NEJM* 2014;371:1189 & 1198)
- Anti-IL-5Rα (**benralizumab**) ↓ steroid use, ↓ exac. in sev asthma w/ eos (*NEJM* 2017;376:2448)
- Anti-IgE (omalizumab) for uncontrolled mod-to-severe allergic asthma (w/ IgE >30) on ICS ± LABA (*JAMA* 2017; 318:279); ↓ exacerbations in severe asthma (*Cochrane* 2014;CD003559)
- Anti-TSLP (tezepelumab-ekko) ↓ exacerbations in severe asthma; can use in non-allergic/non-eosinophilic asthma (*NEJM* 2021;384:1800)
- Allergen ImmunoRx ("allergy shots") may help if sig. allerg. component (*JAMA* 2016;315:1715)

Procedures

- Bronchial thermoplasty: bronchoscopic delivery of thermal energy to airway wall to reduce airway smooth muscle; ↓ exacerb in mod/severe asthma (*Lancet* 2021;9:457)

Exacerbation

Evaluation

- History: baseline PEF, steroid requirement, ED visits, hospital admissions, prior intubation
  Current exacerbation: duration, severity, potential precipitants, meds used
  Risk factors for life-threatening exacerbation: prior intubation, h/o near-fatal asthma, ED visit/hosp for asthma w/in 1 y, current/recent PO steroids, not using ICS, overdependent on SABA, Ψ, h/o noncompliance
- Physical exam: VS, pulm, accessory muscle use, pulsus paradoxus, abdominal paradox Assess for barotrauma: asymmetric breath sounds, tracheal deviation, subcutaneous air → pneumothorax, precordial (Hamman's) crunch → pneumomediastinum
- Diagnostic studies: **peak expiratory flow** (know personal best; <80% personal best c/w poor control, <50% c/w severe exacerbation); **S_aO_2**; **CXR** to r/o PNA or PTX; ABG if severe (low P_aCO_2 initially; nl or high P_aCO_2 *may* signify tiring)

Initial treatment details (GINA 2023 Guidelines)

- **Oxygen** to keep S_aO_2 ≥93–95%
- **Inhaled SABA** (eg, albuterol) by MDI (4–8 puffs) or nebulizer (2.5–5 mg) q20min
- **Corticosteroids:** prednisone 40–60 mg PO × 5–7 d if outPt if in ED or inPt, use methylprednisone 125 mg IV q6h (*NEJM* 1999;340:1941)
- **Ipratropium** MDI (4–6 puffs) or nebulizer (0.5 mg) q20min if severe (*Chest* 2002;121:1977)
- *Reassess after 60–90 min of Rx*
  - Mild–mod exacerbation: cont SABA q1h
  - Sev exacerbation: SABA & ipratropium q1h or cont.; if refractory, consider Mg ± heliox
- *Decide disposition within 4 h of presentation and after 1–3 h of Rx*

ICU-level care (*J Clin Med* 2024;13:859)

- **Noninvasive ventilation:** improves obstruction (*Chest* 2003;123:1018) & ↓ odds of mechanical ventilation and mortality (*AJRCCM* 2020;202:1520); use with caution given potential for worsening hyperinflation and hemodynamic compromise
- **Invasive ventilation:**
  - Large ET tube, P_{plat} <30 cm H_2O (predicts barotrauma better than PIP)
  - Maximize I:E time to minimize auto-PEEP; limited utility of extrinsic PEEP
  - Permissive hypercapnia
  - Paralysis, inhalational anesthetics, bronchoalveolar lavage w/ mucolytic, heliox (60–80% helium), and V/V ECMO have been used with success
  - IV ketamine: bronchodilating effects and can be used for refractory status asthmaticus

Severity of Asthma Exacerbation			
	Mild–Moderate	**Severe**	**Life-Threatening**
Symptoms	Talks in phrases	Talks in words Tripod positioning	Drowsy Confused
Vitals/Exam	RR ≤30, HR 100–120, Room air S_aO_2 90–95%	RR >30, HR >120 Room air S_aO_2 <90%	Silent chest Bradycardia
PEF	>50% predicted or historical best	≤50% predicted or historical best	≤40% predicted or historical best
P_aCO_2	<40 mmHg	Variable	>42 mmHg
Initial Treatment	O_2, SABA 4–10 puffs q20min, PO pred	Transfer to acute facility, SABA, ipratropium, methylpred, IV Mg	
Reassessment *(following 1–3 hours of treatment)*			
Features	PEF >60% Normal exam No distress	PEF <60% Mild/moderate sx RF for near/fatal asthma	PEF <40%
Disposition	Discharge home	Acute care admission	ICU admission
Additional Rx	Inh SABA Oral steroid taper Start daily ICS	q1h SABA + ipratropium Methylpred 125 mg IV q6h	Prepare for intubation Permissive hypercapnia + Mg, ketamine, ? heliox

ANAPHYLAXIS

Definition and pathophysiology (*JACI* 2020;145:1082)

- Severe, rapid onset (mins to hrs), potentially life-threatening syndrome

- Precipitates systemic reactions (bronchospasm, tissue swelling, fluid shifts, vasodilation)

Types & Mechanisms of Anaphylaxis (*Eur J Int Med* 2022;100:5)		
	Pathway	**Common Triggers**
Immunologic	IgE-mediated	Food, insects, meds (eg, NSAIDs, abx, biologics), latex, aeroallergens
	Complement-mediated	Contrast
Non-immunologic	Direct mast cell activation	Drugs (vanco, FQ, opioids)
	Cytokine-mediated	Drugs (mAb, chemotherapy)

Diagnosis: any of the three following criteria:

(1) Acute illness with skin ± mucosal involvement (rash, flushing, hives) AND at least one of:
   (a) respiratory compromise (eg, stridor, hypoxemia) or (b) hypotension/hypoperfusion

(2) Two or more of the following after exposure to a **likely** allergen: skin/mucosal involvement, respiratory compromise, ↓ BP or hypoperfusion, GI symptoms

(3) Hypotension after exposure to **known** allergen for that Pt

- Additional potentially useful laboratory markers: **tryptase** (⊕ if >1.2× baseline +2 ng/mL), but does *not* r/o anaphylaxis if ⊖; serum **histamine** (peaks in 5–15 min)

Treatment

- **Epi:** 0.5 mg IM (0.5 mL of 1 mg/mL solution) q5–15min as needed. For those who do not respond, IV infusion starting at 0.1 µg/kg/min.
- **Airway:** suppl O_2 ± intubation or cricothyroidotomy (if laryngeal edema); β_2-agonists
- Fluid resuscitation w/ ≥1–2 L crystalloid (may extravasate up to 35% of intravasc volume)
- Antihistamines relieve hives & itching, *no effect on airway or hemodynamics*
  H1RA: eg, diphenhydramine 50 mg IV/IM
  H2RA: modest evidence for additional sx relief (*Cochrane* 2014:CD008596)
- Methylprednisolone 1–2 mg/kg/d × 1–2 d for those who do not respond to epi
- Avoid unopposed α-adrenergic vasopressors

Disposition

- Mild rxn limited to urticaria or mild bronchospasm can be observed for ≥6 h; admit all others
- Watch for **biphasic reaction**; occurs in 23%, typically w/in 8–10 h but up to 72 h

Angioedema (*J Allergy Clin Immunol* 2013;131:1491)

- Localized swelling of skin/mucosa; involves face, lips, tongue, uvula, larynx, and bowels
- Etiologies: mast cell-mediated (eg, NSAIDs); bradykinin-mediated (eg, **ACEI,** ARNi, hereditary angioedema, acquired C1 inhibitor deficiency); idiopathic
- Diagnosis: C4 and C1 inhibitor level, tryptase (if suspect anaphylaxis), ESR/CRP
- Rx: intubation if risk of airway compromise. Allergic angioedema: H1/H2 antihist., steroids. If 2° ACEI: d/c ACEI, antihist., icatibant (bradykinin-receptor antag; *NEJM* 2015;372:418) Hereditary angioedema: plasma-derived c1 inhibitor, ecallantide (kallikrein inhibitor)

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Definition and epidemiology (*Lancet* 2022;399:2227)

- Progressive airflow limitation caused by airway and parenchymal inflammation

Emphysema vs. Chronic Bronchitis		
	Emphysema	**Chronic Bronchitis**
Definition	Dilation/destruction of parenchyma (path definition)	Productive cough >3 mo/y × ≥2 y (clinical definition)
Pathophysiology	Tissue destruction V/Q: ↑ dead space fraction → hypercarbia, but only mild hypoxemia	Small airways affected V/Q: ↑ shunt fraction → severe hypoxemia, hypercapnia PHT, cor pulmonale
Clinical manifestations	Severe, constant dyspnea Mild cough	Intermittent dyspnea Copious sputum production
Physical exam	"Pink puffer" Tachypneic, noncyanotic, thin Diminished breath sounds	"Blue bloater" Cyanotic, obese, edematous Rhonchi & wheezes

Pathogenesis (*Lancet* 2017;389:1931)

- **Cigarette smoke** (centrilobular emphysema, affects 15–20% of smokers)
- Recurrent airway infections
- α_1-antitrypsin deficiency: early-onset panacinar emphysema or signif basilar disease, 1–3% of COPD cases. Suspect if age <45, lower lungs affected, extrathoracic manifestations (liver disease [not if heterozygote MZ], FMD, pancreatitis). ✓ serum A1AT level (nb, acute phase reactant).
- Low FEV_1 in early adulthood associated w/ COPD (*NEJM* 2015;373:111)

Clinical manifestations

- Chronic cough, sputum production, dyspnea; later stages → freq exacerb, AM HA, wt loss
- Physical exam: ↑ AP diameter of chest ("barrel chest"), hyperresonance, ↓ diaphragmatic excursion, ↓ breath sounds, ↑ expiratory phase, rhonchi, wheezes
- *Asthma–COPD overlap syndrome* (ACOS; *NEJM* 2015;373:1241): features of both present. For example: reversibility of airway obstruction w/ bronchodilator in COPD; neutrophilic inflammation in asthma (more classic in COPD); eos in COPD.

Diagnostic studies (*JAMA* 2019;321:786)

- CXR (see Radiology inserts): hyperinflation, flat diaphragms, ± interstitial markings & bullae
- PFTs: **obstruction:** ↓↓ FEV_1, ↓ **FVC, FEV_1/FVC <0.7 (no sig Δ post bronchodilator),** expiratory coving of flow-volume loop; **hyperinflation:** ↑↑ RV, ↑ TLC, ↑ RV/TLC; **abnormal gas exchange:** ↓ D_LCO (in emphysema)
- ABG: ↓ P_aO_2, ± ↑ P_aCO_2 (in chronic bronchitis, usually only if FEV_1 <1.5 L) and ↓ pH
- Screen *symptomatic* Pts w/ spirometry; don't screen if asx; screen for α1-AT deficiency

Chronic treatment (adapted from GOLD 2024 Report)

COPD Staging and Recommended Therapies by GOLD Criteria		
Exacerbations/Yr	**Mild Symptoms**	**Mod/Severe Symptoms**
<**2**	**A** bronchodilator	**B** LAMA + LABA
≥**2**	**E** LAMA + LABA Consider adding ICS if blood eosinophils >300	

Smoking cessation & vaccinations in all. Pulm rehab in groups B & E. O_2 as indicated per S_aO_2.

- **Bronchodilators** (*1st-line*)**: long-acting muscarinic antag (LAMA),** β_2-agonists (LABA)
  - LAMA (eg, tiotropium): ↓ exacerb, slows ↓ FEV_1, ↓ admit, ↓ resp failure; better than ipratropium or LABA (*NEJM* 2008;359:1543; 2011;364:1093; 2017;377:923)
  - LABA: ~11% ↓ in exacerbations, no ↑ in CV events (*Lancet* 2016;387:1817)
  - LAMA + LABA: ↑ FEV_1, ↓ sx vs. either alone (*Chest* 2014;145:981) and superior to LABA + inh steroid (*NEJM* 2016;374:2222)
- **Corticosteroids** (inhaled, ICS): ~11% ↓ in exacerbations & slows ↓ FEV_1; no Δ in mortality (*Lancet* 2016;387:1817). Greatest benefit if eos >300 (*Lancet Respir Med* 2018;6:117).
- "Triple Therapy" (LAMA+LABA+ICS) ↓ exac, ↓ hosp, ↑ PNA (*NEJM* 2020;383:35)
- **PDE inhibitors** added to bronchodilators
  - Roflumilast (PDE-4): ↑ FEV_1, ↓ exacerb in sev. COPD & h/o exacerb. (*Lancet* 2015;385:857)
  - Ensifentrine (PDE-3/4): ↓ exacerb, ↑ FEV_1 in mod–severe COPD *(AJRCCM* 2023;208:406)
- Dupilumab (anti-IL-4, IL-13): ↓ exacerb, ↑ FEV_1 if Pts w/ eos >300 (*NEJM* 2023;389:205 & 2024;390:2274)
- Anti-IL-5 (eg, mepolizumab): ↓ exacerb in Pts w/ eos *(NEJM* 2017;377:1613 & 2025;392:1710)
- Antibiotics: daily azithro ↓ exacerbations, but not routine (*JAMA* 2014;311:2225)
- **Oxygen:** if P_aO_2 ≤55 mmHg or S_aO_2 ≤89% (during rest, exercise, or sleep) to prevent cor pulmonale; only Rx proven to ↓ mortality (*Annals* 1980;93:391; *Lancet* 1981;i:681); no benefit in Pts w/ moderate hypoxemia (S_aO_2 89–93%) (*NEJM* 2016;375:1617) or nocturnal O_2 alone (*NEJM* 2020;383:1129); unknown benefit of isolated exertional O_2 (*AJRCCM* 2020;202:121)
- Night NIV if recent exacerb & P_aCO_2 >53 ↓ risk of readmit or death (*JAMA* 2017;317:2177)
- **Prevention:** Flu/Pneumovax; smoking cessation → 50% ↓ in lung function decline (*AJRCCM* 2002;166:675) and ↓ long-term mortality (*Annals* 2005;142:223)
- Rehabilitation: ↓ dyspnea and fatigue, ↑ exercise tolerance, ↑ QoL (*NEJM* 2009;360:1329)
- Surgery & bronchoscopic interventions
  - Bronchoscopic lung reduction w/ endobronchial valves or coils: ↑ lung fxn but significant complications (PTX, PNA) (*NEJM* 2015;373:2325; *Lancet* 2015;386:1066; *JAMA* 2016;315:175)
  - Lung volume reduction surgery: ↑ exercise capacity, ↓ mortality *if* FEV_1 >20%, upper lobe, low exercise capacity (*NEJM* 2003;348:2059)
- Lung transplant: ↑ QoL & ↓ sx (*Lancet* 1998;351:24), ? survival benefit (*Am J Transplant* 2009;9:1640)

Staging and prognosis

- Assess breathlessness, cough, sputum, exercise capacity, & energy (tools such as CAT and mMRC may be used as part of assessment)
- Ratio of diam PA/aorta >1 associated with ~3× ↑ risk of exacerbations (*NEJM* 2012;367:913)
- FEV_1 stages: I = ≥80%; II = 50–79% (~11% 3-y mort.); III = 30–49% (~15% 3-y mort.); IV = <30% (~24% 3-y mort.)

Exacerbation

- Exacerbation triggers: infection, other cardiopulmonary disease, including PE
  - Infxn: overt tracheobronchitis/pneumonia from viruses, *S. pneumoniae, H. influenzae, M. catarrhalis* or triggered by changes in strain of colonizers (*NEJM* 2008;359:2355).
- Physical exam: wheezes, tachypnea, accessory muscle use, pulsus paradoxus, cyanosis

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COPD Exacerbation Treatment		
Agent	**Dose**	**Comments**
Ipratropium	MDI 4–8 puffs q1–2h *or* Nebulizer 0.5 mg q1–2h	First-line therapy (*NEJM* 2011;364:1093)
Albuterol	MDI 4–8 puffs q1–2h *or* Nebulizer 2.5–5 mg q1–2h	Benefit if component of reversible bronchoconstriction
Corticosteroids	Prednisone 40 mg/d × 5 d (*JAMA* 2013;309:2223); some will benefit from higher dose/longer course if severe Methylprednisolone 125 mg IV q6h × 72 h for more severe exacerbations	↓ treatment failure, ↓ hosp. stay ↑ FEV_1 but no mortality benefit, ↑ complications (*Cochrane* 2009:CD001288) OutPt Rx after ED visit ↓ relapse (*NEJM* 2003;348:2618) Consider limiting use if eos ≥2% (*Lancet Respir Med* 2024;12:67)
Antibiotics	Amox, TMP–SMX, doxy, azithro, antipneumococcal FQ all reasonable (no single abx proven superior). Consider local flora and avoid repeat courses of same abx. ≤5 d course likely enough for mild–mod exacerbation (*JAMA* 2010;303:2035).	*H. flu, M. catarrhalis, S. pneumo* ↑ PEF, ↓ Rx failure, ? ↓ short-term mort, ↓ subseq exacerb (*Chest* 2008;133:756 & 2013;143:82) Consider if CRP >20 + ↑ sputum purulence or CRP >40 (*NEJM* 2019;381:111)
Oxygenation	↑ F_iO_2 to achieve P_aO_2 ≥55–60 *or* S_aO_2 88–92%	**Watch for CO_2 retention** (due to ↑ V/Q mismatch, loss of hypoxemic resp drive, Haldane effect)*, but must maintain acceptable S_aO_2!*
Noninvasive ventilation	Initiate *early* if moderate/severe dyspnea, ↓ pH/↑ P_aCO_2, RR >25 Results in 58% ↓ intubation, ↓ LOS by 3.2 d, 59% ↓ mortality Contraindications: Δ MS, inability to cooperate or clear secretions, hemodynamic instability, UGIB (*NEJM* 1995;333:817; *Annals* 2003;138:861; *Cochrane* 2004;CD004104; *ERJ* 2005;25:348) Pt receiving high-intensity (TV 10–15 mL/kg) vs. low-intensity (6–10 mL/kg) NIV less likely to meet criteria for intubation (*JAMA 2024;332:1709)*	
Endotracheal intubation	Consider if P_aO_2 <55–60, ↑'ing P_aCO_2, ↓'ing pH, ↑ RR, respiratory fatigue, Δ MS or hemodynamic instability	
Other	Monitor for arrhythmias; no use for mucolytics (*Chest* 2001;119:1190)	
Post-exacerb care	Follow-up w/in 1 mo; smoking cessation if current smoker; vaccinations (influenza, pneumococcal, SARS-CoV-2, RSV), referral to pulm rehab, consider need for nocturnal NIV (*AJRCCM* 2007;176:532)	

SOLITARY PULMONARY NODULE

Principles

- Definition: single, well-defined, <3 cm, surrounded by nl lung, no LAN or pleural effusion
- Often "incidentalomas," esp with ↑ CT use, but may still be early, curable malignancy

Etiologies	
Benign (70%)	**Malignant (30%)**
Granuloma (80%): TB, histo, coccidio **Hamartoma** (10%) Bronchogenic cyst, AVM, pulm infarct Echinococcosis, ascariasis, aspergilloma GPA, rheumatoid nodule, sarcoidosis Lipoma, fibroma, amyloidoma	**Bronchogenic carcinoma** (75%) periph: adeno (most common) & large cell central: squamous & small cell **Metastatic** (20%): sarcoma, melanoma, breast, head & neck, colon, testicular, renal Carcinoid, primary sarcoma

Initial evaluation

- **History:** h/o cancer, smoking, age (<30 y = 2% malignant, +15% each decade >30)
- **CT:** size/shape, Ca^{2+}, LAN, effusions, bony destruction, **compare w/ old studies** Ø Ca → ↑ likelihood malignant; laminated → granuloma; "popcorn" → hamartoma
- High-risk features for malig: size (eg, ≥2.3 cm diameter), spiculated, upper lobe, ♀, >60 yo, >1 ppd current smoker, no prior smoking cessation (*NEJM* 2013;369:910)

Diagnostic studies

- **PET:** detects metab. activity of tumors, 97% Se & 78% Sp for malig (esp if >8 mm). Useful to decide bx vs. serial CT & for surgical staging b/c may detect mets.
- **Transthoracic needle biopsy** (TTNB): if tech feasible, 97% will obtain definitive tissue dx
- **Video-assisted thoracoscopic surgery** (VATS): for percutaneously inaccessible lesions; highly sensitive and allows resection
- **Transbronchial bx** (TBB): most lesions too small to sample w/o endobronchial U/S; bronch w/ brushings low-yield unless invading bronchus; navigational bronch 70% yield
- PPD, fungal serologies, ANCA

Management (*JAMA* 2022;327:264)

- **Low risk** (<5%): serial CT (freq depending on risk); shared decision w/ Pt re: bx
- **High risk** (and surgical candidate): TBB, TTNB, or VATS → lobectomy if malignant
- **Subsolid nodules:** longer f/u (b/c if malignant can be slow-growing) & PET

Follow-Up Imaging for Solid Nodules (*Radiographics* 2018;38:1337)				
#	Pt Risk	Nodule <6 mm	Nodule 6–8 mm	Nodule >8 mm
Single	Low	No routine f/u	CT at 6–12 mo, consider at 18–24 mo	CT at 3 mo, consider PET/CT or bx
	High	CT at 12 mo?	CT at 6–12 & 18–24 mo	
Multi	Low	No routine f/u	CT at 3–6 mo, consider at 18–24 mo	CT at 3–6 mo, consider at 18–24 mo
	High	CT at 12 mo?	CT at 3–6 & 18–24 mo	CT at 3–6 & 18–24 mo

HEMOPTYSIS

Definition and pathophysiology

- Expectoration of blood or blood-streaked sputum
- **Massive hemoptysis:** >100 mL/h or >500 mL in 24 h; massive hemoptysis usually from tortuous or invaded bronchial arteries

Etiologies (*Crit Care Med* 2000;28:1642)	
Infection/ Inflammation	**Bronchitis** (most common cause of trivial hemoptysis) **Bronchiectasis** incl **CF** (common cause of massive hemoptysis) TB or aspergilloma (can be massive); pneumonia or lung abscess
Neoplasm	Usually primary **lung cancer**, sometimes metastasis (can be massive)
Cardiovasc	**PE** (can be massive), pulmonary artery rupture (2° to instrumentation), CHF, mitral stenosis, trauma/foreign body, bronchovascular fistula
Other	**Vasculitis** (GPA, anti-GBM, Behçet's, SLE), AVM, anticoag (w/ underlying lung disease), coagulopathy, cocaine, pulm hemosiderosis

Diagnostic workup

- Localize bleeding site (r/o *GI or ENT source* by H&P ± endo); determine whether **unilateral or bilateral, localized or diffuse, parenchymal or airway** by CXR/chest CT ± bronch
- PT, PTT, CBC to rule out **coagulopathy**
- Sputum culture/stain for bacteria, fungi, and AFB; cytology to **r/o malignancy**
- ANCA**,** anti-GBM, ANA, urinalysis to ✓ for **vasculitis** or **pulmonary-renal syndrome**

Treatment

- **Death is from asphyxiation not exsanguination**; maintain gas exchange, reverse coagulopathy and Rx underlying condition; cough suppressant may ↑ risk of asphyxiation
- Inhaled tranexamic acid promising (*Chest* 2018;154:1379)
- Massive hemoptysis: **put bleeding side dependent;** selectively intubate nl lung if needed
  Angiography: Dx & Rx (vascular occlusion balloons or **selective embol of bronch. art**)
  Rigid bronch: allows more options (electrocautery, laser) than flexible bronch
  Surgical resection

BRONCHIECTASIS

Definition and epidemiology (*NEJM* 2022;387:533)

- Obstructive airways disease of bronchi and bronchioles, chronic transmural inflammation w/ airway dilatation and thickening, collapsibility, mucus plugging w/ impaired clearance

Initial workup

- H&P: cough, dyspnea, copious sputum production, ±hemoptysis, inspiratory "squeaks"
- CXR: scattered or focal; rings of bronchial cuffing; "tram track" of dilated, thick airways
- PFTs: obstructive; chest CT: airway dilation & thickening ± cystic Δs, infiltrates, adenopathy

Etiology	Other Features	Evaluation
Chronic infxns (eg, MTb, ABPA)	Chronic cough, freq/persist infiltrate, refract asthma (ABPA)	Sputum cx (incl mycobact, fungal), ± bronch/BAL, IgE, & eos (ABPA)
1° ciliary dyskin	Sinusitis, infertility, otitis	Dynein mutations
Immunodefic	Recurrent infxns often as child	IgA, IgG, IgM, IgG subclasses
RA, Sjögren, ANCA	Resp sx may precede joint sx	RF, CCP, SS-A, SS-B, ANCA
IBD	Not relieved by bowel resection	Colonoscopy, biopsy
α_1-AT deficiency	Lower lobe emphysema	α_1-AT level and genotype
Anatomic	R middle lobe synd. from sharp takeoff, foreign body aspiration	Bronchoscopy

Treatment

- Acute exacerbations: antibiotics directed against prior pathogens; if no prior Cx data → FQ. Avoid azithro given high risk for non-TB mycobacteria and potential need for Rx.
- Chronic mgmt: treat underlying condition, chest PT, inhaled hypertonic saline, bronchodil.; brensocatib (DPP-1 inhib) ↓ exacerb (*NEJM* 2025;392:1569); prophylactic azithro in non-CF
- Airway clearance: guaifenesin, instrumental devices (eg, Aerobika, Acapella), chest PT, percussion devices

Non-tuberculous mycobacterium (NTM; eg, MAC, ***Mycobacterium kansasii***)

- Chronic cough, ↓ wt; Lady Windermere syndrome: R middle lobe and lingula bronchiectasis in elderly ♀ who suppress expectoration
- Dx: CT scan (tree-in-bud, nodules, cavities, bronchiect.), sputum ×3 or BAL, AFB stain + Cx
- Treatment: susceptibility-based Rx pref over empiric Rx w/ [azithro or clarithro] + rifamycin & ethambutol for ≥12 mo (*CID* 2020;71:e1)

CYSTIC FIBROSIS

Definition and pathophysiology (*NEJM* 2023;389:1693)

- Autosomal recessive genetic disorder due to mutations in chloride channel (*CFTR* gene)
- ↑ mucus thickness, ↓ mucociliary clearance, ↑ infections → bronchiectasis

Clinical features

- Recurrent PNA, sinus infections
- Distal intestinal obstruction syndrome (DIOS), pancreatic insufficiency (steatorrhea, malabsorption, failure to thrive, weight loss), CF-related diabetes, infertility

Treatment (*Lancet* 2021;397:2195)

- Acute exacerbations: may be assoc w/ persistent drop in FEV_1 (*AJRCCM* 2010;182:627); continue aggressive airway clearance, target abx based on sputum cx (incl double coverage for PsA); common pathogens include PsA, *S. aureus*, non-typeable *H. flu*, *Stenotrophomonas*, *Burkholderia*, NTM
- Chronic mgmt: airway clearance with chest PT, inhaled hypertonic saline, inhaled DNAse (dornase alfa), SABA; oral azithromycin if chronic respiratory symptoms, inhaled tobramycin or aztreonam if persistent PsA infection
- CFTR potentiator (ivacaftor) or corrector (lumacaftor, tezacaftor) depending on mutation; combo (elexacaftor+tezacaftor+ivacaftor) if homozygous for ΔF508 (*Lancet* 2019;394:1940)
- Lung transplantation; refer to lung transplant center when FEV_1 <30% predicted, rapidly declining FEV_1, 6MWT <400 m, evidence of PHT, significant clinical decline

INTERSTITIAL LUNG DISEASE

WORKUP OF ILD (*JAMA* 2024;331:1655)

May present as incidental finding, subacute dyspnea, or rapidly progressive hypox. resp fail.

Broad categories

- (1) **Sarcoid**; (2) **Exposures** (eg, drugs, XRT, organic & inorganic dusts, vaping); (3) **Collagen vasc dis** (eg, scleroderma, ANCA, myositis, RA); (4) **Idiopathic PNAs**

Rule out mimickers of ILD

- **Congestive heart failure** (✓ NT-proBNP, trial of diuresis); **infxn:** viral, atypical bacterial; **malignancy:** lymphangitic carcinomatosis, lung adenocarcinoma, leukemia, lymphoma

History and physical exam

- Occupational, exposures (eg, birds), tobacco, meds, XRT, FHx, precipitating event
- Tempo (acute → infxn, CHF, hypersens pneumonitis, eos PNA, AIP, COP, drug-induced, e-cigarette or vaping)
- Extrapulm signs/sx (skin Δs, arthralgias, arthritis, myalgias, sicca sx, alopecia, Raynaud's)

Diagnostic studies (see Appendix & Radiology inserts)

- CXR and **high-resolution chest CT**
  - Upper lobe predom: hypersensitivity, coal, silica, smoking-related, sarcoidosis, Langerhans
  - Lower lobe predom: NSIP, UIP, asbestosis
  - Adenopathy: malignancy, sarcoidosis, berylliosis, silicosis
  - Pleural disease: collagen vascular diseases, asbestosis, infections, XRT
- PFTs: ↓ D_LCO (*early sign*), restrictive pattern (↓ volumes), ↓ P_aO_2 (esp. w/ exercise)
  - If restrictive + obstructive, consider sarcoid
  - If combined pulmonary fibrosis and emphysema (CFPE) → near-nl lung vol on PFTs
- Serol.: ACE, ANA, RF, RNP, ANCA, CCP, SSA/SSB, Scl-70, CK, aldolase, myositis panel
- Bronchoalveolar lavage: in select cases if suspect superimposed infection, hemorrhage, eosinophilic syndromes, hypersensitivity pneumonitis (BAL lymphocytes >35%)
- Bx (cryobiopsy vs. VATS depending on location) if unclear etiology

Specific Etiologies of ILD

Sarcoidosis (*AJRCCM* 2020;201:e26; *JAMA* 2022;327:856)

- Prevalence: African Americans, northern Europeans, and females; onset in 3rd–5th decade
- Pathophysiology: depression of cellular immune system peripherally, activation centrally

Clinical Manifestations of Sarcoidosis	
Organ System	**Manifestations**
Pulmonary	Hilar LAN; fibrosis; pulm hypertension. Stages: I = bilat hilar LAN; II = LAN + ILD; III = ILD only; IV = diffuse fibrosis.
Cutaneous (~15%)	Waxy skin plaques; lupus pernio (violaceous facial lesions) Erythema nodosum (red tender nodules due to panniculitis, typically on shins). Ddx: idiopathic (34%), infxn (33%, strep, TB), sarcoid (22%), drugs (OCP, PCNs), vasculitis (Behçet's), IBD, lymphoma.
Ocular (10–30%)	Anterior > posterior uveitis; ↑ lacrimal gland
Endo & renal (10%)	Nephrolithiasis, hypercalcemia (10%), hypercalciuria (40%) Due to vitamin D hydroxylation by macrophages
Neuro (10% clin, 25% path)	CN VII palsy, periph neuropathies, CNS lesions, seizures
Cardiac (5% clin, 25% path)	Conduction block, arrhythmia, cardiomyopathy
Liver, spleen, BM	Granulomatous hepatitis (25%), splenic & BM gran. (50%)
Constitutional	Fever, night sweats, anorexia, & wt loss (a/w hepatic path)
Musculoskeletal	Arthralgias, periarticular swelling, bone cysts

- *Löfgren's syndrome:* erythema nodosum + hilar adenopathy + arthritis (good prognosis)
- Diagnostic studies: **LN bx → noncaseating granulomas** + multinucleated giant cells
  Endobronchial ultrasonography superior to conventional bronch (*JAMA* 2013;309:2457) ^{18}FDG PET can be used to identify extent and potentially targets for dx bx ↑ **ACE** (Se 60%, 90% w/ active dis., Sp 80%, false ⊕ in granulomatous diseases)
- To assess extent: CXR, PFTs, full ophtho exam, ECG, CBC (lymphopenia, ↑ eos), Ca, LFTs; ± Holter, echo, cardiac MRI, brain MRI, etc., based on s/s
- Rx: **steroids** if sx or extrathoracic organ dysfxn (eg, prednisone 20–40 mg/d), improves sx, but doesn't Δ long-term course; hydroxychloroquine for extensive skin disease; MTX, AZA, mycophenolate, or anti-TNF for chronic/refractory disease
- Prognosis: ~2/3 spontaneously remit w/in 10 y (60–80% of stage I, 50–60% stage II, 30% stage III), w/ relapses uncommon; ~1/3 have progressive disease

Exposure

- **Drugs/Iatrogenic**
  Amiodarone: interstitial pneumonitis ↔ org. PNA ↔ ARDS; Rx: d/c amio; steroids
  Other drugs: nitrofurantoin, sulfonamides, INH, hydralazine
  Chemo: bleomycin, busulfan, cyclophosphamide, MTX, immunotherapy, XRT
- **Pneumoconioses** (inorganic dusts) (*NEJM* 2000;342:406; *Clin Chest Med* 2004;25:467)
  Coal worker's: upper lobe predominant, may progress to massive fibrosis

Silicosis: upper lobe opacities ± eggshell calcification of lymph nodes; ↑ risk of TB
Asbestosis: lower lobe fibrosis & calcified pleural plaques. Asbestos exposure also associated w/ pleural plaques & thickening, mesothelioma, lung cancer.
Berylliosis: multisystemic granulomatous disease that mimics sarcoidosis

- **Hypersensitivity pneumonitides** (organic dusts): loose, *noncaseating granulomas*
  Antigens: farmer's lung (spores of thermophilic actinomyces); bird fancier's lung (proteins from feathers and excreta of birds or down); humidifier lung (thermophilic bacteria)

Collagen vascular diseases (*Chest* 2013;143:814)

- **Rheumatologic disease** (*ILD biggest cause of morbidity and mortality*)
  Scleroderma: ILD in ~50%; PHT seen in ~10% of Pts with limited disease
  PM–DM: ILD & skin/muscle findings; MCTD: PHT & fibrosis; Sjögren's: ILD & sicca sx
  SLE & RA: pleuritis and pleural effusions more often than ILD; SLE can cause DAH
- **Vasculitis** (can p/w *DAH*)
  Granulomatosis w/ polyangiitis (GPA): ⊕ c-ANCA w/ necrotizing granulomas
  Eosinophilic GPA (EGPA): ⊕ c- or p-ANCA w/ eosinophilia & necrotizing granulomas
  Microscopic polyangiitis: ⊕ p-ANCA w/o granulomas
- **Goodpasture's syndrome** = DAH + RPGN; typically in smokers; ⊕ anti-GBM in 90%
- **Lymphangioleiomyomatosis** (LAM): cystic, ↑ in ♀, Rx w/ sirolimus (*NEJM* 2011;364:1595)
- **Lymphoid interstitial PNA (LIP):** proliferation of polyclonal lymphocytes/plasma cells associated w/ Sjögren's and other CTD, immunodeficiencies

Idiopathic interstitial pneumonias (IIPs) (*AJRCCM* 2013;188:733)

- Definition: **ILD of unknown cause;** dx by radiographic, histologic, and clinical features

IIPs		
Type	**Imaging/Histology**	**Clinical**
IPF	UIP imaging pattern: reticular opacities, honeycombing, traction bronchiectasis; peripheral, subpleural, & basal	Sx >12 mo 5-y mort ~80%
NSIP	Homogeneous ground-glass opacities or consolid., reticular irreg lines; subpleural sparing; symmetric, peripheral, basal. Cellular & fibrotic subtypes.	Sx mos–y 5-y mort 10%
COP	Patchy, migratory consolidations; subpleural & peribronchial. Excessive proliferation of granulation tissue in small airways and alveolar ducts.	Post-infxn, XRT, rxn to drug. 5-y mort <5%
AIP	Diffuse ground-glass opacities, consolidations w/ lobular sparing. Path/imaging similar to DAD (diffuse, bilateral, central > periph ground-glass or consolidative opacities).	Sx <3 wk 6-mo mort 60%
DIP	Diffuse ground-glass opacities, reticular lines; lower zones. Peripheral macrophage in alveoli.	30–50 yo *smokers* Sx wks–mos Death rare
RB-ILD	Bronchial thickening, centrilobular nodules, patchy ground-glass opacities; upper lobe predom. Mφ in alveoli.	

UIP, usual interstitial PNA (IP); IPF, idiopathic pulm fibrosis; NSIP, nonspecific IP; COP, cryptogenic organizing PNA; AIP, acute IP; DIP, desquamative IP; RB-ILD, resp bronchiolitis-assoc ILD

- Mgmt: suppl O_2, pulm rehab, GERD Rx, PHT screening, lung txp referral if severe
- IPF Rx: **antifibrotics** pirfenidone or nintedanib ↓ FVC decline (*NEJM* 2014;370:2083 & 2019;381:1718) (can consider for fibrotic NSIP); controlled-release morphine to ↓ cough (*Lancet Resp Med* 2024;12:273); high-dose steroids for acute exac., no RCT data
- Smoking cessation can be curative for DIP & RB-ILD
- Steroids for NSIP (esp. cellular type), COP, LIP; ? benefit for AIP & DIP/RB-ILD

- MMF + rituximab for CTD-ILD or NSIP (*Eur Resp J* 2023;61:2202071)

Pulmonary infiltrates w/ eosinophilia (PIE) · eos on BAL and/or peripheral blood

- **Allergic bronchopulmonary aspergillosis (ABPA) or EGPA** (qv)
- Löffler's syndrome: parasites/drugs → transient pulm infilt + cough, fever, dyspnea, eos
- Acute eosinophilic PNA (AEP): acute hypox febrile illness; Rx: steroids, tobacco cessation
- Chronic eosinophilic pneumonia (CEP): "photonegative" of CHF, typically in women

Miscellaneous

- Pulm alveolar proteinosis (PAP): accumulation of surfactant-like phospholipids; milky BAL
- Langerhans cell histiocytosis (LCH): young ♂ smokers; apical cysts; PTX (25%)

PLEURAL EFFUSION

Pathophysiology

- **Systemic factors** (eg, ↑ PCWP, ↓ oncotic pressure) → *transudative* effusion
- **Local factors** (ie, Δ pleural surface permeability) → *exudative* effusion

Transudates

- **Congestive heart failure** (**40%**): 80% bilateral, ± cardiomegaly on CXR occasionally exudative (especially after aggressive diuresis or if chronic)
- **Constrictive pericarditis** (knock on exam, calcification or thickening on imaging)
- **Cirrhosis** ("hepatic hydrothorax"): diaphragmatic pores allow passage of ascitic fluid often right-sided (²/₃) & massive (even w/o marked ascites)
- Nephrotic syndrome: usually small, bilateral, asymptomatic (r/o PE b/c hypercoag)
- Other: PE (usually exudate), malignancy (lymphatic obstruction), myxedema, CAPD

Exudates

- **Lung parenchymal infection (25%)** (*Chest* 1995;108:299)
  - Bacterial (parapneumonic): can evolve along spectrum of *exudative* (but sterile if uncomplicated) → *fibropurulent* (infected fluid) → *organization* (fibrosis & formation of rigid pleural peel). Common causes: *Strep pneumo, Staph aureus, Klebsiella, PsA, Haemophilus, Bacteroides, Peptostreptococcus*, mixed flora in aspiration pneumonia.
  - Mycobacterial: >50% lymphs 80% of the time, ADA >40, pleural bx ~70% Se
  - Fungal, viral (usually small), parasitic (eg, amebiasis, echinococcosis, paragonimiasis)
- **Malignancy** (**15%**): primary lung cancer most common, metastases (esp. breast, lymphoma, etc.), mesothelioma (✓ serum osteopontin levels; *NEJM* 2005;353:15)
- **Pulmonary embolism** (**10%**): effusions in ~40% of PEs; exudate (75%) > transudate (25%); hemorrhagic—*must have high suspicion b/c presentation highly variable*
- **Collagen vascular disease:** RA (large), SLE (small), GPA, EGPA
- **Abdominal diseases:** pancreatitis, cholecystitis, esophageal rupture, abdominal abscess
- Hemothorax (Hct_{eff}/Hct_{blood} >50%): trauma, PE, malignancy, coagulopathy, leaking aortic aneurysm, aortic dissection, pulmonary vascular malformation
- Chylothorax (triglycerides >110): thoracic duct damage due to trauma, malignancy, LAM
- Other:
  - Post-CABG: left-sided; initially bloody, clears after several wks
  - Dressler's syndrome (pericarditis & pleuritis post-MI), uremia, post-radiation therapy

Asbestos exposure: benign; ⊕ eos
Drug-induced (eg, nitrofurantoin, methysergide, bromocriptine, amiodarone): ⊕ eos
Meigs' syndrome: benign ovarian tumor → ascites & pleural effusion
Yellow nail syndrome: yellow nails, lymphedema, pleural effusion, bronchiectasis

Initial diagnostic studies (*NEJM* 2018;378:740)

- **Thoracentesis** (ideally U/S guided) (*NEJM* 2006;355:e16)
  Indications: **all effusions >1 cm in decubitus view**
  if suspect due to CHF, can diurese and see if effusions resolve (75% do so in 48 h); *asymmetry, fever*, *chest pain, or failure to resolve* → thoracentesis
  parapneumonic effusions should be tapped ASAP (*cannot* exclude infxn clinically)
  Diagnostic studies: ✓ total protein (TP), LDH, glucose, cell count w/ differential, Gram stain & culture, pH, cholesterol; additional studies as dictated by clinical scenario
  Complications: PTX (5–10%), hemothorax (~1%), reexpansion pulm edema (if >1.5 L removed), spleen/liver lac.; post-tap CXR not routinely needed (*Annals* 1996;124:816). Risk of bleed low w/ U/S & experienced operator even if INR ~1.9, on DOAC, or on clopi (*Mayo* 2019;94:1535).

Transudative vs. Exudative Effusions (*JAMA* 2014;311:2422)	
Light's Criteria	**Three-Test Rule**
$TP_{effusion}/TP_{serum}$ >0.5 $LDH_{effusion}/LDH_{serum}$ >0.6 $LDH_{effusion}$ > 2/3 ULN of LDH_{serum}	$Chol_{effusion}$ >55 mg/dL $LDH_{effusion}$ >200 U/L $Chol_{effusion}/Chol_{serum}$ >0.3
More sensitive: Meeting 1 qualif ies. If 2 criteria met, 97% Se, 85% Sp for exudate.	**More specific:** Any single criterion >85% Sp for exudative effusion (only 70–95% Se)

- In CHF, $TP_{effusion}$ *may* ↑ *with diuresis or chronicity* → "pseudoexudate"; $chol_{eff}$ useful
- In parapneumonic: **complicated** = ⊕ Gram stain or culture *or* pH <7.2 *or* glucose <60. Usually req. tube thoracostomy for resolution. **Empyema** = frank pus. Req. tube thoracostomy for resolution.
- Chest CT

Additional pleural fluid studies (*NEJM* 2002;346:1971)

- NT-proBNP ≥1500 pg/mL has 91% Se & 93% Sp for CHF (*Am J Med* 2004;116:417)
- WBC & diff.: exudates tend to have ↑ WBC vs. transudates but nonspecific
  neutrophils → parapneumonic, PE, pancreatitis
  lymphocytes (>50%) → cancer, TB, rheumatologic
  eos (>10%) → blood, air, drug rxn, asbestos, paragonimiasis, Churg–Strauss, PE
- RBC: Hct_{eff} 1–20% → cancer, PE, trauma; Hct_{eff}/Hct_{blood} >50% → hemothorax
- AFB: yield in TB 0–10% w/ stain, 11–50% w/ culture, ~70% w/ pleural bx
- Adenosine deaminase (ADA): seen w/ granulomas, >70 suggests TB, <40 excludes TB
- Cytology: ideally ≥150 mL and at least 60 mL should be obtained (*Chest* 2010;137:68)
- Glucose: <60 mg/dL → malignancy, infection, RA
- Amylase: seen in pancreatic disease and esophageal rupture (salivary amylase)
- Rheumatoid factor, C_H50, ANA: *limited utility* in dx collagen vascular disease
- Triglycerides: >110 → chylothorax, 50–110 → ✓ lipoprotein analysis for chylomicrons
- Creatinine: effusion/serum ratio >1 → urinothorax
- Fibulin-3: ↑ plasma and/or effusion levels → mesothelioma (*NEJM* 2012;367:1417)

Undiagnosed persistent effusions

- Transudate: most commonly CHF or hepatic hydrothorax. ✓ s/s CHF or cirrhosis, NT-proBNP$_{eff}$; consider intraperitoneal injection of technetium-99m sulfur colloid.
- Exudate (*Clin Chest Med* 2006;27:309): most commonly malig, empyema, TB, PE. ✓ s/s malig, chest CT (I^+), ADA or IFN-γ release assay; consider thoracoscopy.
- Consider pleural biopsy for unresolving effusion with no clear cause

Characteristics of Pleural Fluid (not diagnostic criteria)

Etiology	WBC Diff	pH	Glc	Comments
CHF	<1000 *lymphs*	nl	≈ serum	bilateral, cardiomegaly, NT-proBNP ↑↑
Cirrhosis	<1000	nl	≈ serum	right-sided
Uncomplicated parapneumonic	5–40,000 *polys*	nl to ↓	≈ serum (>40)	
Complicated parapneumonic	5–40,000 *polys*	↓↓	↓↓ (<40)	requires drainage
Empyema	25–100,000 *polys*	↓↓↓	↓↓	frank pus; requires drainage
Tuberculosis	5–10,000 *lymphs*	nl to ↓	nl to ↓	⊕ AFB ⊕ ADA
Malignancy	1–100,000 *lymphs*	nl to ↓	nl to ↓	⊕ cytology
Pulmonary embolism	1–50,000 *polys*	nl	≈ serum	usually exudative, esp if associated infarction
Rheumatoid arthritis/SLE	1–20,000 *variable*	↓	RA ↓↓↓ SLE nl	↑ RF, ↓ C_H50 ↑ imm. complex
Pancreatitis	1–50,000 *polys*	nl	≈ serum	left-sided, ↑ amylase
Esophageal rupture	<5000 >50,000	↓↓↓	↓↓	left-sided, ↑ amylase
Chylothorax	1–100,000 *lymphs*	nl	≈ serum	milky appearance, TG >100 mg/dL
Hemothorax	n/a	nl	≈ serum	bloody, Hct_{eff}/Hct_{blood} >50%

Treatment

- Symptomatic effusion: therapeutic thoracentesis, treat underlying disease process
- Parapneumonic effusion (*Chest* 2000;118:1158)
  uncomplicated → antibiotics for pneumonia
  >1⁄2 **hemithorax** or **complicated** or **empyema** → **tube thoracostomy** (otherwise risk of organization and subsequent need for surgical decortication)
  loculated→ tube thoracostomy or VATS; intrapleural tPA + DNase ↓ need for surgery
- Malignant effusion: serial thoracenteses vs. tube thoracostomy + pleurodesis (success rate ~80–90%) vs. indwelling pleural catheter, which ↓ hosp days but ↑ adverse events (*JAMA* 2017;318:1903); systemic steroids & pH <7.2 a/w ↑ pleurodesis failure rate
- TB effusions: effusion will often resolve spontaneously; however, treat Pt for active TB
- Hepatic hydrothorax
  Rx: Δ pressure gradient (ie, ↓ ascitic fluid volume, NIV)

avoid chest tubes; prn thoracenteses, pleurodesis, TIPS or VATS closure of diaphragmatic defects if medical Rx fails; NIV for acute short-term management
spontaneous bacterial empyema (SBEM) can occur (even w/o SBP being present), ∴ thoracentesis if suspect infection
liver transplant is definitive treatment and workup should begin immediately

VENOUS THROMBOEMBOLISM (VTE)

Definitions

- Superficial thrombophlebitis: pain, tenderness, erythema along superficial vein
- Deep venous thrombosis (DVT): ***Proximal*** = thrombosis of iliac, femoral, or popliteal veins (nb, "superficial" femoral vein part of deep venous system). ***Distal*** = calf veins below knee; lower risk of PE/death than proximal (*Thromb Haem* 2009;102:493).
- Pulmonary embolism (PE): thrombosis originating in venous system and embolizing to pulmonary arterial circulation; 1 case/1000 person y; 250,000/y (*Archives* 2003;163:1711)

Risk factors

- Virchow's triad. **Stasis:** bed rest, inactivity, CHF, CVA w/in 3 mo, air travel >6 h. **Injury to endothelium:** trauma, surgery, prior DVT, inflam, central catheter.
  Thrombophilia: genetic disorders (qv), HIT, OCP, HRT, tamoxifen, raloxifene.
- Malignancy (12% of "idiopathic" DVT/PE; *Circ* 2013;128:2614)
- History of thrombosis (greater risk of recurrent VTE than genetic thrombophilia)
- Obesity, smoking, acute infection, postpartum (*JAMA* 1997;277:642; *Circ* 2012;125:2092)

Thromboprophylaxis (*Blood Adv* 2018;2:3198)

Patient & Situation	Prophylaxis
Low-risk med; same-day surg & <40 y	Early, aggressive ambulation ± mechanical
Mod (hosp., ≥1 risk factor) or high-risk medical (ICU, cancer, stroke)	**LMWH** or **UFH** (if renal failure) or fonda (if HIT ⊕). Pharmacologic favored vs. mechanical, but may personalize based on bleeding & thrombotic risk.
Low-risk surgery (minor surgery)	Mechanical Ppx
Moderate-risk surgery (eg, major surgery, trauma, immobilization)	If low bleeding risk: **LMWH** pref over **UFH** SC If high bleeding risk: **mech Ppx**
High-risk nonortho surgery (mult. risk factors), immobil. stroke, or ICH	**[LMWH** or **UFH** SC**]** + **mech**. Stroke s/p lytic or ICH: mech 24 h or until bleed stable, then + pharm.
Ortho surgery (cont pharmacoRx up to 35 d [hip] or 10–14 d [knee])	**LMWH** or **DOAC** (or fonda, UFH, or warfarin [INR 2–3]) + **mech Ppx**

UFH: 5000 U SC bid or tid. Enox 40 mg qd or 30 mg bid if higher-risk, Riva 10 mg/d, apixa 2.5 mg/d, edox 30 mg/d.

Clinical manifestations—DVT

- Calf pain, swelling (>3 cm c/w unaffected side), venous distention, erythema, warmth, tenderness, palpable cord, ⊕ Homan's sign (calf pain on dorsiflexion, seen in <5%)
- 50% of Pts with sx DVT have asx PE
- Popliteal (Baker's) cyst: may lead to DVT due to compression of popliteal vein

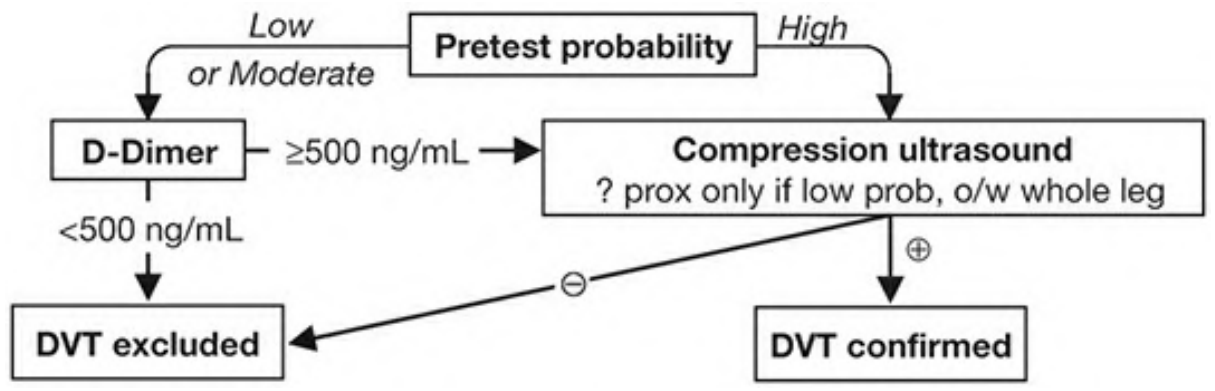
Modified Wells Pretest Probability Scoring of DVT (With permission from *Lancet* 1997;350:1795.)		
+1 point each for: active cancer (Rx ongoing or w/in 6 mo or palliative); paralysis, paresis, or recent immobilization of lower extremities; recently bedridden for ≥3 d or major surgery w/in 12 wk; localized tenderness along distribution of deep venous system; entire leg swelling; calf ≥3 cm larger than asx calf (at 10 cm below tibial tuberosity); pitting edema confined to sx leg; collateral superficial veins (nonvaricose); previous DVT –2 points if alternative dx at least as likely as DVT		
Pretest Probability Assessment (useful if outPt, less so if inPt; *JAMA IM* 2015;175:1112)		
Score ≤0	**Score 1 or 2**	**Score ≥3**
Low probability (5%)	**Moderate probability (17%)**	**High probability (53%)**

- For UE DVT, +1 point each for venous cath, local pain, & unilateral edema, –1 if alternative dx. ≤1 = unlikely; ≥2 = likely. U/S if likely or if unlikely but abnl D-dimer (*Annals* 2014;160:451).

Diagnostic studies—DVT

- D-dimer: <500 helps r/o; ? use 1000 as threshold if low risk (*Annals* 2013;158:93)
- Compression U/S >95% Se & Sp for sx DVT (lower if asx); survey whole leg if ≥ mod prob

Figure 2-2 Approach to suspected DVT



Clinical manifestations—PE

- Dyspnea (~50%), pleuritic chest pain (~40%), cough (~23%), hemoptysis (~8%)
- ↑ RR (>70%), crackles (51%), ↑ HR (30%), fever, cyanosis, pleural friction rub, loud P_2
- *Massive:* syncope, HoTN, PEA; ↑ JVP, R-sided S_3, PR murmur

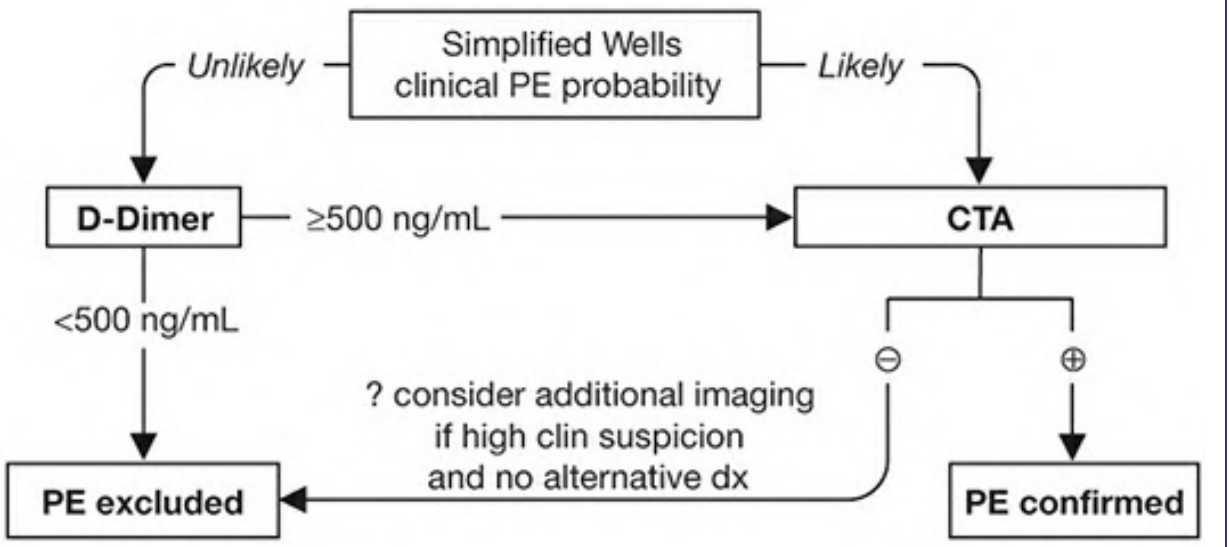
Modified Wells Pretest Probability Scoring for PE (*Ann Intern Med* 2011;154(11):709–718. Reprinted with the permission of American College of Physicians.)	
• Prior PE or DVT = 1.5 points • Active cancer = 1.0	• Clinical signs of DVT = 3

• Immobilization (bed rest ≥3 d) or surgery w/in 4 wk = 1.5 • Alternative dx less likely than PE = 3	• HR >100 bpm = 1.5 • Hemoptysis = 1.0
Simplified Wells Probability Assessment	
≤4 = "Unlikely" (13% probability)	**>4 "Likely" (39% probability)**

Diagnostic studies—PE (*EHJ* 2014;35:3033)

- CXR (limited Se & Sp): 12% nl, atelectasis, effusion, ↑ hemidiaphragm, Hampton hump (wedge-shaped density abutting pleura); Westermark sign (avascularity distal to PE)
- ECG (limited Se & Sp): sinus tachycardia, AF; signs of RV strain → RAD, P pulmonale, RBBB, $S_IQ_{III}T_{III}$ (McGinn–White pattern; *JAMA* 1935;104:1473), TWI V_1–V_4
- ABG: hypoxemia (only 18% nl), hypocapnia, resp. alk., ↑ A-a gradient (only 6% nl)
- D-dimer: high Se, poor Sp (~25%); ELISA has >99% NPV, ∴ use to r/o PE if "unlikely" pretest prob (*JAMA* 2006;295:172); cut-off 500 if <50 y, 10× age if ≥50 y (*JAMA* 2014;311:1117)
- Echocardiography: useful for risk stratification (RV dysfxn), but not dx (Se <50%)
- V/Q scan: high Se (~98%), low Sp (~10%). Sp improves to 97% for high-prob VQ. Use if pretest prob of PE high and CT not available or contraindicated.
- **CT angiography** (CTA; see Radiology inserts; *JAMA* 2015;314:74): Se ~90% & Sp ~95%; PPV & NPV >95% if imaging concordant w/ clinical suspicion, ≤80% if discordant (∴ need to consider both); ~1/4 of single & subseg may be false ⊕; CT may also provide other dx
- Lower extremity compression U/S shows DVT in ~9%, sparing CTA

Figure 2-3 Approach to suspected PE



Workup for idiopathic VTE (*NEJM* 2015;373:697)

- **Thrombophilia workup:** ✓ if ⊕ FH; useful for relatives or if dx APLAS (Rx requires warfarin over other AC). During acute thrombosis, genetic tests (Factor V Leiden and prothrombin gene mutation) and tests for APLAS (qv) reliable; coag factor testing not.
- **Malignancy workup:** 12% Pts w/ "idiopathic" DVT/PE will have malignancy; age-appropriate screening adequate; avoid extensive w/u

Risk stratification for Pts with PE

- **Clinical**: Simplified PE Severity Index (sPESI) risk factors include age >80 y; h/o cancer; h/o cardiopulm. disease; HR ≥110; SBP <100; S_aO_2 <90%
- **Imaging**: TTE for RV dysfxn; CTA for RV/LV dimension ratio >0.9. **Biomarker**: Tn & BNP.
- **Classification** (*EHJ* 2020;41:543)
  High risk ("massive"): hemodyn unstable w/ arrest, obstructive shock, or persistent HoTN
  Intermediate risk ("submassive"): sPESI ≥1
  "Intermediate-high" if *both* RV dysfunction & elevated Tn
  "Intermediate-low" if *either* or *neither* RV dysfunction nor elevated Tn
  Low risk: clinically stable, sPESI = 0, normal RV function, normal Tn

Whom to treat (*JAMA* 2020;324:1765; *Chest* 2021;160:e545)

- **Superficial venous thrombosis:** elevate extremity, warm compresses, compression stockings, NSAIDs for sx. *Anticoag* if high risk for DVT (eg, ≥5 cm, proximity to deep vein ≤5 cm, other risk factors) for 4 wk as ~10% have VTE w/in 3 mo (*Annals* 2010;152:218).
- **LE DVT:** Prox → a/c. Distal → a/c vs. serial imaging over 2 wk to see if extends.
- **UE DVT:** anticoagulate (same guidelines as LE; *NEJM* 2011;364:861). If catheter-associated, need not remove if catheter functional and ongoing need for catheter.
- **PE:** anticoagulate (unless isolated subsegmental and risk for recurrent VTE low)

Initial Anticoagulation Options (*EHJ* 2020;41:543; *Chest* 2021;160:e545; *NEJM* 2022;387:45)

Initiate immediately if high suspicion but dx will take ≥4 h; a/c safe if plt >50k
DVT & low-risk PE w/o comorbidities and able to comply with Rx can be treated as outPt

Class	Dose	Comment
LMWH	Enox 1 mg/kg SC q12h Dalteparin 200 IU/kg SC qd	Preferred over UFH (espec. if cancer) except if CrCl <25, extreme obesity or hemodynamic instability. First line in preg.
UFH	80 U/kg IVB → 18 U/kg/h; titrate to aPTT 1.5–2.3 × baseline	Preferred when considering lysis or catheter-based Rx
DOAC	Apixa 10 mg bid × 7 d → 5 mg bid Riva 15 mg qd × 21 d → 20 mg/d	Facilitates transition to outPt Rx. Not rec. if hemodynamically unstable.

If HIT: fondaparinux 5–10 mg qd, bivalirudin 0.15 mg/kg/h (renally adjusted) → titrate to aPTT 1.5–2.5× baseline, or argatroban 2 μg/kg/min → titrate to aPTT 1.5–3.0× baseline

Reperfusion therapy options (*JACC* 2020;76:2117)

- *Several different options for severe, high-risk PE*
- Systemic thrombolysis: typically full dose, but also ↓ dose options to ↓ risk of bleeding
- Catheter-based therapies: suction removal of clot, fragmentation of clot, directed lytic
- Surgical embolectomy

Systemic thrombolysis (*EHJ* 2020;41:543; *Chest* 2021;160:e545)

- Typically TPA 100 mg over 2 h or wt-adjusted TNK bolus; risk of ICH ~2–5%, ↑ w/ age
- Consider if low bleed risk w/ acute PE + HoTN or cardiopulm deterioration after anticoag
- If cardiac arrest thought likely due to PE, consider tPA 50 mg IVB ± repeat 30 min later
- **High-risk PE:** ↓ death & recurrent PE each by ~50% (*JAMA* 2014;311:2414; *EHJ* 2015;36:605)
- **Intermediate-risk PE:** ↓ hemodyn decompensation, ↑ ICH & major bleeding, ↓ mortality in short- but not long-term; ? consider if <75 y and/or low bleed risk (*JAMA* 2014;311:2414)
- *Half-dose lytic* (50 mg or 0.5 mg/kg if <50 kg; 10-mg bolus → remainder over 2 h) in ~intermed.

PE: ↓ pulm HTN & ? PE or death w/ ≈ bleeding vs. heparin alone (*AJC* 2013;111:273)
- **DVT:** consider if (a) acute (<14 d) & extensive (eg, iliofemoral), (b) severe sx swelling or ischemia, and (c) low bleed risk

Mechanical intervention (*JACC* 2020;76:2117)

- **Catheter-based clot extraction** (eg, AngioVac or FlowTriever): consider if intermediate-risk and hemodyn. compromise **or** high risk & not candidate for systemic lysis or surgical thrombectomy (*Circ* 2014;129:479). Preferred to systemic lytic by some centers. ↓ clinical deterioration vs. cath-directed lysis w/o mortality benefit (*Circ* 2025;151:260).
- **Catheter-directed** pharmacomech: low-dose lytic infused (eg, tPA 1 mg/h for 12–24 hr per catheter) + U/S or mech fragmentation of clot
- **Surgical embolectomy:** if large, proximal PE + hemodynamic compromise + contraindic. to lysis; consider in experienced ctr if large prox. PE + RV dysfxn
- **IVC filter:** use if anticoag contraindic.; no benefit to adding to anticoag (*JAMA* 2015;313:1627)
  Complications: migration, acute DVT, ↑ risk of recurrent DVT & IVC obstruction (5–18%)

Duration of full-intensity anticoagulation

- Superficial venous thrombosis: 4 wk
- Distal DVT: ~3 mos ↓ risk of recurrence vs. 6 wks (*BMJ* 2022;379:e072623)
- 1st prox DVT *or* PE 2° reversible/time-limited risk factor *or* distal DVT: 3–6 mo
- 1st *unprovoked* prox DVT/PE: ≥3 mo, then reassess; benefit to prolonged Rx. Consider clot, bleed risk, Pt preference, and intensity of Rx when crafting strategy.
- 2nd VTE event or cancer: indefinite (or until cancer cured) (*NEJM* 2003;348:1425)

Long-term anticoagulation options

- For nonpregnant Pt w/o severe renal dysfunction or active cancer → DOAC
- For severe renal insuffic. or APLAS → warfarin. Parenteral a/c bridge to INR ≥2 × ≥24 h.
- Pregnancy or unable to take oral therapy → LMWH or fondaparinux
- Cancer → DOAC (but in Pts w/ UGI cancers, more GI bleeding w/ riva) or LMWH

Extended DOAC strategies (*NEJM* 2013;368:699; 2017;376:1211; 2025;392:1363; *Lancet* 2025;405:725)

- After ≥6 mo of anticoag, following regimens compared w/ no extended Rx (or ASA):
- Full-dose DOAC: 80–90% ↓ recurrent VTE, 2–5× bleeding, no signif excess in major bleed
- 1⁄2 dose apixa or riva: ≥75% ↓ recur. VTE, w/o ↑ bleeding. Non-inferior to full dose & less bleeding.

Complications & prognosis

- Postthrombotic syndrome (23–60%): pain, edema, venous ulcers
- Recurrent VTE: 1%/y (after 1st VTE) to 5%/y (after recurrent VTE)
- Chronic thromboembolic PHT after acute PE ~2–3%, consider thromboendarterectomy
- Mortality: ~10% for DVT and ~10–15% for PE at 3–6 mo (*Circ* 2008;117:1711)

PULMONARY HYPERTENSION (PHT)

PHT defined as PA mean pressure ≥20 mmHg at rest (*ERJ* 2019;53:1801913)
PA mean = CO × PVR + PA wedge pressure. Trans pulm gradient = PA mean − PA wedge.

Etiologies (Revised WHO Classification) (*Eur Respir J* 2022;43:3618)	
Primary pulmonary arterial HTN (PAH) (group 1) Precapillary PHT PCWP ≤15 mmHg ↑ transpulm grad ↑ PVR	• Idiopathic (IPAH): yearly incidence 1–2 per million; mean age of onset 36 y (♂ older than ♀); ♂: ♀ = ~2: • Familial (FPAH) • Associated conditions (APAH) Connective tissue dis.: CREST, SLE, MCTD, RA, PM, Sjögren Congenital L→R shunts: ASD, VSD, PDA Portopulmonary HTN (? 2° vasoactive substances not filtered in ESLD; ≠ hepatopulmonary syndrome) HIV; drugs & toxins: anorexic agents, SSRIs, L-tryptophan • Pulmo veno-occlusive disease: ? 2° chemo, BMT; orthopnea, pleural eff, CHF, nl PCWP; art vasodilators *worsen* CHF • Pulmonary capillary hemangiomatosis
Left heart disease (group 2). ↑ PCWP	• Left atrial or ventricular (diastolic or systolic) dysfunction • Left-sided valvular heart disease (eg, MS/MR)
Lung diseases and/or chronic hypoxemia (group 3)	• COPD • ILD • Sleep apnea • Alveolar hypoventilation (eg, NM disease) • Chronic hypoxemia (eg, high altitude) • Developmental abnormalities
Chronic thrombo- embolic dis (group 4)	• Prox or distal PEs; ~1⁄2 w/o clinical h/o PE (*NEJM* 2011;364:351) • Nonthrombotic emboli (tumor, foreign body, parasites)
Miscellaneous/ Multifactorial (group 5)	• Sarcoidosis, histiocytosis X, LAM, schistosomiasis, ESRD • Compression of pulm vessels (adenopathy, tumor, fibrosing mediastinitis, histoplasmosis, XRT) • Other: thyroid dis., glycogen storage dis., Gaucher dis, HHT, sickle cell, etc., chronic myeloprolif d/o, splenectomy

Clinical manifestations

- Dyspnea, exertional syncope (hypoxia, ↓ CO), exertional chest pain (RV ischemia)
- Symptoms of R-sided CHF (eg, peripheral edema, RUQ fullness, abdominal distention)
- WHO class: I = asx w/ ordinary activity; II = sx w/ ord. activ.; III = sx w/ min activ.; IV = rest sx

Physical exam

- PHT: prominent P_2, R-sided S_4, RV heave, PA tap & flow murmur, PR (Graham Steell), TR
- ± RV failure: ↑ JVP, hepatomegaly, peripheral edema

Diagnostic studies & workup (*JAMA* 2022;327:1379)

- High-res chest CT: dilat. & pruning of pulm arteries, ↑ RA & RV; r/o parenchymal lung dis.
- ECG: RAD, RBBB, RAE ("P pulmonale"), RVH (Se 55%, Sp 70%)
- PFTs: disproportionate ↓ D_LCO, mild restrictive pattern; r/o obstructive & restrictive lung dis.
- ABG & polysomnography: ↓ P_aO_2 and S_aO_2 (espec w/ exertion), ↓ P_aCO_2, ↑ A-a gradient; r/o hypoventilation and OSA
- TTE: ↑ RVSP (but estimate over/under by ≥10 mmHg in 1⁄2 of PHT Pts; *Chest* 2011;139:988)
  ↑ RA, RV, & PA; ↑ pressure → interventricular septum systolic flattening ("D" shape)
  ↓ RV systolic fxn (TAPSE <1.6 cm); TR, PR; r/o LV dysfxn, MV, AoV, congenital disease
- RHC: ↑ RA, RV, & PA pressures; ✓ L-sided pressures and for shunt
  if PAH: nl PCWP, ↑ transpulmonary gradient (mean PAP-PCWP >12–15), ↑ diastolic pulmonary gradient (PA diastolic − PCWP >7), ↑ PVR, ± ↓ CO
  if 2° to L-heart disease: PCWP (or LVEDP) >15; if PVR nl → "passive PHT"; PVR >240 suggests mixed picture: if ↓ PCWP → ↓ PVR, then "reactive" PHT; if no Δ, then "fixed"
- CTA (large/med vessel), V/Q scan (small vessel to r/o CTEPH), ± pulm angio if ↑ concern
- Labs: ANA (~40% ⊕ in PAH), anti-Scl-70, anti-RNP; LFTs; HIV
- 6-min walk test (6MWT) or cardiopulmonary exercise testing to establish fxnl capacity

Treatment (*Eur Heart J* 2022;43:3618; *JAMA* 2022;327:1379)

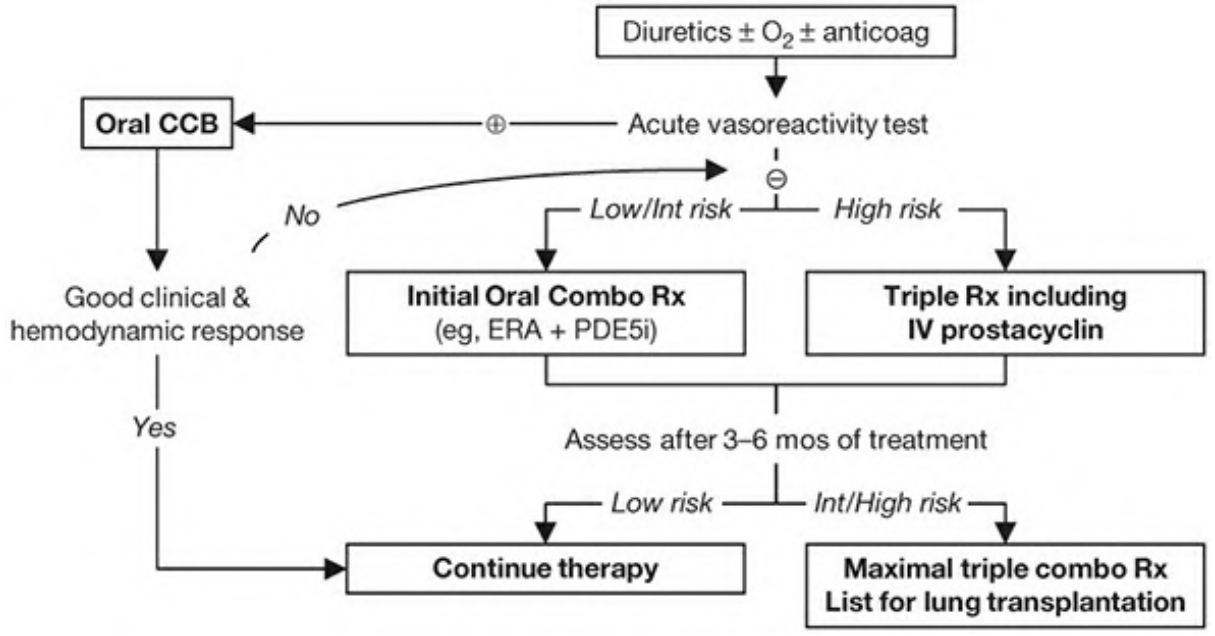
- Principles: (1) prevent & reverse vasoactive substance imbalance and vascular remodeling (2) prevent RV failure: ↓ wall stress (↓ PVR, PAP, RV diam); ensure adeq systemic DBP
- **Supportive**
  Oxygen: maintain S_aO_2 >90–92% (reduces vasoconstriction)
  Diuretics: ↓ RV wall stress and relieve RHF sx; *gentle* b/c RV is preload dependent
  Anticoag: critical in CTEPH, otherwise not routinely used
- Supervised exercise training; aggressive apnea/hypoventilatory Rx w/ CPAP/BiPAP
- **Vasodilators** (ideally right heart catheterization prior to initiation): many different options
- Risk strat. (low, intermed, high) based on R-sided HF sx, syncope, WHO fxnal class, 6MWT, CPET, NT-proBNP, imaging, hemodyn. (RAP <8, 8–14, >14; CI ≥2.5, 2–2.4, <2)

Treatment	**Comments** (data primarily in Group 1)
PDE-5 inhibitor sildenafil, tadalafil, vardenafil	↑ cGMP → vasodilatation, ↓ smooth muscle proliferation, ↓ sx, ↑ 6MWT, no data on clinical outcomes. Often 1st line b/c minimal side-effect profile: HA, vision Δ's, sinus congestion.
Endothelin receptor antagonists (ERAs) bosentan, ambrisentan, macitentan	↓ Smooth muscle remodeling, vasodilatation, ↓ fibrosis, ↓ sx, ↑ 6MWT, ↓ worsening PAH or need for prostanoids w/ trend for ↓ PAH mortality (w/ macitentan). Side effects: ↑ LFTs, HA, anemia, edema, teratogen (*NEJM* 2013;369:809).
IV prostacyclin epoprostenol (Flolan)	Vasodilatation, ↓ plt agg, ↓ smooth muscle prolif; benefits ↑ w/ time (? vasc remodeling). ↑ 6MWT, ↑ QoL, ↓ **mortality**. Side effects: HA, flushing, jaw pain, abd cramps, N/V, diarrhea, catheter infxn.
Prostacyclin analogs [iloprost (inh), treprostinil (IV, inh, SC)]	Same mech as prostacyclin IV, but easier admin, ↓ side effects, w/o risk of catheter infxn. ↓ sx, ↑ 6MWT. Inh Rx w/ improved V/Q matching. Inh treprostinil ↑ 6MWT in ILD-PH (*NEJM* 2021;384:325).
Prostacyclin receptor agonist (selexipag, PO)	Indicated for Group I to delay disease progression and risk of hospitalization. Add in WHO FC II & III (NEJM 2015;373:2522).
Soluble guanylate cyclase stimulator riociguat	NO-independent ↑ cGMP → vasodilatation, ↓ smooth muscle proliferation, ↓ sx, ↑ 6MWT in PAH; ↓ sx, ↓ PVR, ↑ 6MWT in CTEPH (*NEJM* 2013;369:319 & 330)
TGF-α ligand inhibitor sotatercept	↓ PVR, ↑ 6MWT, improved WHO fxnal class, ↓ clinical worsening or **mortality** (*NEJM* 2023;388:1478 & 2025;392:1987). ↓ plt & epistaxis.

Oral CCB nifedipine, diltiazem	Consider if ⊕ acute vasoreactive response. Not 1st line b/c side effects: HoTN, lower limb edema.

- Acute vasoreactivity test: use inh NO, adenosine or prostacyclin to identify Pts likely to have long-term response to CCB (⊕ response = ↓ PAP ≥10 mmHg to <40 mmHg w/ ↑ or stable CO); ~10% Pts acute responders; no response → still candidate for other vasodil. Rx
- Vasoreactive → CCB. If fxnal class IV, treat as if nonreactive per below.
- Nonreactive: upfront combo (ERA + PDE5i) superior to monoRx (*NEJM* 2015;373:834)
- Fxnal class IV → combo Rx including parental prostanoid
- Treat underlying causes of 2° PHT; can use vasodilators, although little evidence
- CTEPH: riociguat. Pulm endarterectomy potentially curative (*AJRCCM* 2011;183:1605) vs. balloon pulmonary angioplasty in nonoperative Pts (*Circ Outcomes* 2017;10:e004029).
- Refractory PHT: balloon atrial septostomy: R→L shunt causes ↑ CO, ↓ S_aO_2, net ↑ tissue O_2 delivery; lung txp (single or bilateral; heart–lung needed if Eisenmenger physiology)

Figure 2-4 Treatment of PAH (Modified from *Eur Heart J* 2022;43:3618)



Management of ICU patient

- Avoid tachyarrhythmias & overly aggressive volume resuscitation
- Caution w/ vasodilators if any L-sided dysfunction
- *Intubation can cause hemodynamic collapse*
- Dobutamine and inhaled NO or prostacyclin; consider R-sided mechanical support
- Consider fibrinolysis if acute, refractory decompensation (eg, TPA 50 mg IVB ± repeat)

Prognosis

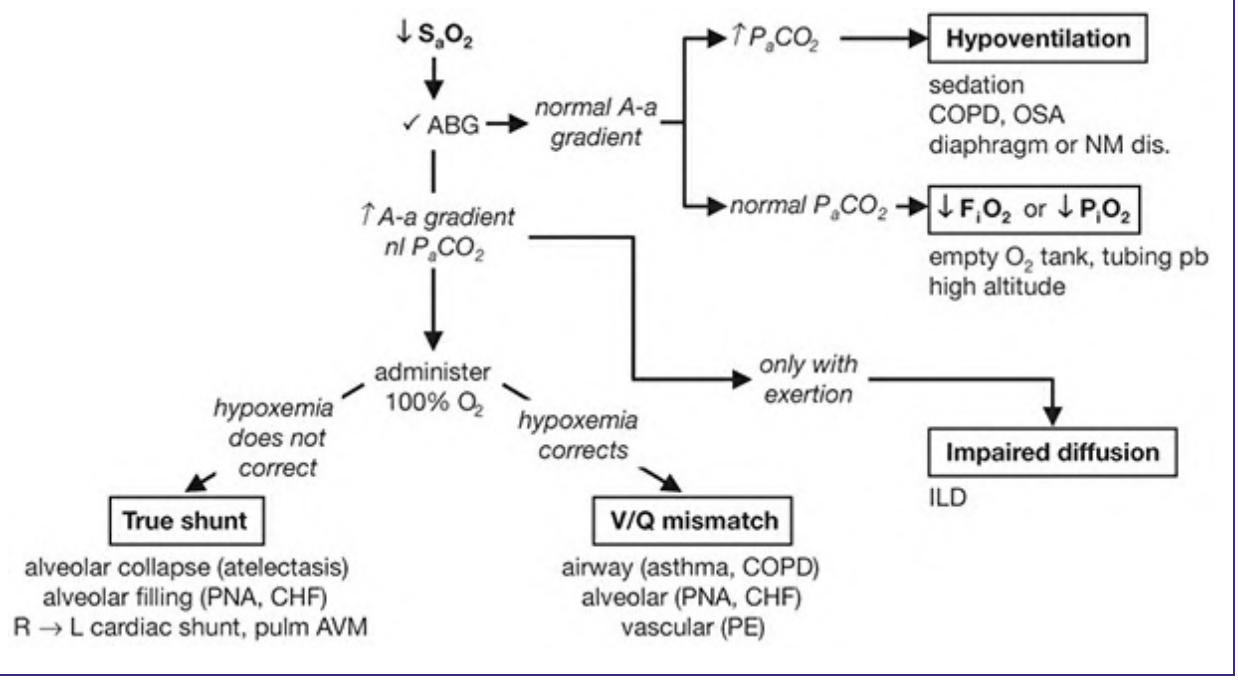
- Median survival after dx ~2.8 y; PAH (all etiologies): 2-y 66%, 5-y 48% (*Chest* 2004;126:78S)
- Poor prognostic factors: clinical evidence of RV failure, rapidly progressive sx, WHO (modified NYHA) class IV, 6MWT <300 m, peak VO_2 <10.4 mL/kg/min, ↑ RA or RV or RV dysfxn, RA >20 or CI <2.0, ↑ BNP (*Chest* 2006;129:1313)

RESPIRATORY FAILURE

Chemical Causes of Cellular Hypoxia						
Condition	**Causes**	**Classic Features**	**P_aO_2**	**Pulse Ox**	**CO-Ox sat**	**Treatment (+ 100% O_2)**
Carbon monoxide	Fires, portable heaters, auto exhaust	Cherry-red skin (COHb color)	nl	nl	↓	Hyperbaric O_2
Methemo-globinemia	Nitrates, sulfonamide, benzocaine, dapsone	Chocolate brown blood	nl	mild ↓ ~85%	↓	Methylene blue
Cyanide	Nitroprusside, fires, industrial	Bitter almond odor; pink skin	nl	nl (↑ S_vO_2)	nl	Hydroxo-cobalamin

- **A-a gradient** = **P_AO_2** − **P_aO_2:** normal (*on room air*) = "4 + age/4" or "2.5 + (0.2 × age)"
- Hypoxemia + nl A-a gradient: problem is ↓ P_iO_2/F_iO_2 or ↑ P_aCO_2 (ie, hypoventilation)
- Hypoxemia + ↑ A-a gradient: problem is either
  - **R → L shunt**, anatomic (congenital heart dis) or severe pathophys (alveoli filled w/ fluid; eg, PNA, pulm edema); cannot overcome w/ 100% O_2 b/c of sigmoidal Hb-O_2 curve
  - **V/Q mismatch** where "shunt-like" areas (↓ V & nl Q) cause unoxygenated blood to mix with oxygenated blood; can be overcome w/ ↑ O_2 delivery
  - Diffusion limitation: generally seen with exercise/↑CO

Figure 2-5 Workup of acute hypoxemia



- **Cyanosis:** when >5 g/dL of deoxygenated Hb in vessels of skin/mucous membranes. Central: ↓ S_aO_2 (pulm disease, shunt); abnl Hb [metHb, sulfHb, COHb (not true cyanosis)] Peripheral: ↓ blood flow → ↑ O_2 extraction (eg, ↓ CO, cold, arterial or venous obstruction)

Chemical Causes of Cellular Hypoxia						
Condition	**Causes**	**Classic Features**	**P_aO_2**	**Pulse Ox**	**CO-Ox sat**	**Treatment (+ 100% O_2)**
Carbon monoxide	Fires, portable heaters, auto exhaust	Cherry-red skin (COHb color)	nl	nl	↓	Hyperbaric O_2
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Cyanide	Nitroprusside, fires, industrial	Bitter almond odor; pink skin	nl	nl (↑ S_vO_2)	nl	Hydroxo-cobalamin

CO binds to Hb more avidly than does O_2. Pulse oximeter (Ox) misreads COHb as HbO_2 → falsely nl sat.
Oxidizing drugs Δ Hb (ferrous) to MetHb (ferric), which cannot carry O_2. Pulse ox misreads MetHb as HbO_2.
Cyanide inhibits mitochondrial O_2 use → cellular hypoxia but pink skin and ↑ *venous* O_2 sat.

$$\text{Hypercapnia} \rightarrow P_A CO_2 = k \times \frac{\dot{V}CO_2}{RR \times (V_T - V_D)}$$

Etiologies of High ↑ P_aCO_2			
"Won't Breathe"	**"Can't Breathe"**		
↓ RR	**↓ V_T**		**↑ V_D and/or ↓ V_T**
Respiratory Drive	**NM System**	**CW/Pleura**	**Lung/Airways**
Voluntary hypervent. Nl PI_{max} & A-a grad	↓ PI_{max} ↓ PE_{max}	**Abnl PEx** **Abnl CT**	**Abnl PFTs** ↓ End-tidal CO_2
Metabolic alkalosis **1° neurologic:** brain-stem stroke, tumor, 1° alveolar hypovent **2° neurologic:** sedatives, CNS infxn, hypothyroidism	**Neuropathies:** cervical spine, phrenic nerve, GBS, ALS, polio **NMJ:** MG, LE **Myopathies:** diaphragm PM/DM, ↓ PO_4, musc dystrophies	**Chest wall:** obesity, kyphosis, scoliosis **Pleura:** fibrosis effusion	**Lung parenchyma:** emphysema, ILD/fibrosis, CHF, PNA **Airways:** asthma, COPD, OSA, CF bronchiectasis

↑ VCO_2 typically transient cause of ↑ P_aCO_2; Ddx: exercise, fever, hyperthyroidism, ↑ work of breathing, ↑ carbs.

MECHANICAL VENTILATION

Indications

- Improve gas exchange: ↑ oxygenation, ↑ alveolar vent and/or reverse acute resp acidosis
- Relieve respiratory distress: ↓ work of breathing (can account for up to 50% of total O_2 consumption), ↓ respiratory muscle fatigue

- Apnea, airway protection, pulmonary toilet

Supportive Strategies Prior to Intub. or After Extub.

Oxygen Delivery Systems (*Lancet* 2016;387:1867)		
System or Device	**O_2 Flow[a]**	**F_iO_2 Range & Comments**
Low-flow nasal cannula	**1–6**	24–40%, 1 L adds ~3% F_iO_2
Standard face mask	**5–10**	35–50%, minimum 5 L/min
Partial rebreather mask	**>10**	40–70%
Nonrebreather mask	**>10**	60–80% (not 100% b/c air leaks)
Air-entrainment mask (Venturi or Venti mask)	10–15[b]	24–50%, F_iO_2 stays constant
High-flow nasal cannula (HFNC) (*NEJM* 2015;372: 2185; *JAMA* 2015;313:2331; 2016;315:1354; 2025;333:875)	**≤40**	21–100%. In nonhypercapnic acute hypoxemic resp failure, ± ↓ intub. (espec if P_aO_2/F_iO_2 ≤200) & ↓ 90-d mort vs. stnd O_2. ≅ to NIV. Routine use after extub. ↓ need for reintub.

[a]L/min. [b]Total airflow >60 L/min. (Adapted from Marino PL. *The ICU Book*, 4th ed, 2014:431)

Noninvasive Ventilation (NIV) (*NEJM* 2022;387:1688)	
Indications (*Lancet* 2009;374:250)	*Clinical:* mod–severe dyspnea, RR >24–30, signs of ↑ work of breathing, accessory muscle use, abd paradox *Gas exchange:* P_aCO_2 >45 mmHg (& significantly worse than baseline), hypoxemia, P_aO_2/F_iO_2 <200
Contraindications (*Crit Care Med* 2007;35:2402)	Claustrophobia, poor mask fit, Δ**MS**, vomiting, **cannot protect airway**, extrapulm organ failure, HD instab, sev UGIB, ↑ secretions
Continuous positive airway pressure (CPAP)	≈ PEEP. Pt breathes spont. at own rate while vent maintains constant positive airway pressure throughout respiratory cycle. No limit on O_2 delivered (ie, can give hi-flow → F_iO_2 ≈1.0) Used if primary problem ***hypoxemia*** (eg, CHF)
Bilevel positive airway pressure (BiPAP)	≈ PSV + PEEP. Able to set both inspiratory (usually 8–10 cm H_2O) and expiratory pressures (usually <5 cm H_2O). Used if primary problem *hypoventilation*; F_iO_2 delivery limited
Mask ventilation (? helmet better; *JAMA* 2016;315:2435)	Tight-fitting mask connecting patient to a standard ventilator Can receive PS ~20–30 cm H_2O, PEEP ~10 cm H_2O, F_iO_2 ~1.0 Used for short-term support (<24 h) for a reversible process
Conditions w/ strong evidence	**Cardiogenic pulmonary edema:** may ↓ intub. ± mortality (*JAMA* 2005;294:3124; *Lancet* 2006;367:1155; *NEJM* 2008;359:142) **COPD exac.** w/ ↑ P_aCO_2: ↓ intub. & mort., but if pH <7.3 → intubate Acute hypoxemic resp failure: ↓ intub. & mortality (*JAMA* 2020;324:57) High-risk extub. (>65 y, CHF, APACHE II >12): NIV × 24 h directly after extub. → ↓ reintub. and, if P_aCO_2 >45 mmHg during SBT, ↓ mortality. Does not Δ total # vent days (*JAMA* 2018;320:1881). Hypoxemic resp failure after abdominal surgery: ↓ reintubation **Immunosupp.** w/ infiltrates: ↓ complications & mortality

Ventilator Management

Ventilator Modes and Principles (*NEJM* 2001;344:1986; *Chest* 2015;148:340)	
Cont mandatory ventilation (CMV), aka assist control (AC)	Vent delivers a minimum number of supported breaths Additional Pt-initiated breaths trigger *fully assisted* vent breaths ∴ Vent-triggered breaths identical to Pt-triggered breaths Tachypnea → ? resp. alkalosis, breath-stacking, & auto-PEEP May be pressure targeted or volume targeted (qv)
Pressure support vent (PSV)	Support Pt-initiated breaths w/ a set inspiratory pressure & PEEP A mode of *partial* vent support because no set rate
Other	Synch intermittent mand. vent: deliver min # supported breaths; V_T of additional Pt-initiated breaths determined by Pt's effort Proportional assist ventilation (PAV): delivers variable pressure to achieve targeted % of work of breathing

Volume or Pressure Targeted	
Volume targeted	Vent delivers a set V_T; pressures depend on airway resist. & lung/CW compl. **Benefit:** ↑ control over ventilation (ideal initial ventilator setting); benefit in ALI/ARDS; easy to measure mechanics (PIP, P_{plat}, airway resist., compl.) Volume control (VC) ⊕: vent delivers variable pressure (depending on real-time lung compliance) to achieve set V_T
Pressure targeted	Vent delivers a fixed inspiratory pressure regardless of V_T V_T depends on airway resistance and lung/chest wall compliance **Benefit:** may ↑ Pt comfort requiring less sedation
General principles	**Institutional/practitioner preference** and **Pt comfort** usually dictate ventilator strategy; no strategy has proven superior **Alarms** can be set for ↓ or ↑ volumes and ↑ airway pressures in pressure-targeted and volume-targeted strategies, respectively **Risks:** volutrauma (ie, overdistention, if set volume too high; *NEJM* 2013;369:2126), barotrauma [can happen w/ relatively high set volumes (espec if stiff lungs) or if pressure target set too high; key is to monitor transpulmonary pressure (difference between P_{plat} and esophageal ≈ intrapleural), not just airway pressure]; can result in PTX, pneumomediastinum **Hypo-/hyperventilation:** need to ✓ minute vent & pH/P_aCO_2

Variables on the Ventilator	
F_iO_2	Fraction of inspired air that is oxygen
V_T (tidal vol)	Volume of breath delivered; lung-protective ventilation: goal ≤6 mL/kg IBW If no ARDS, similar # of vent days at higher V_T (*JAMA* 2018;320:1872)
f (resp. rate)	Rate set by ventilator, f may be lower than RR if Pt triggering breaths. Adjust to achieve desired P_aCO_2.
Positive end-expiratory pressure (PEEP)	Positive pressure applied during exhalation via resistor in exhalation port Benefits: prevents alveolar collapse, ↓ shunt, ↑ O_2 via alveolar recruitment and improved compliance, allows severely obstructed Pt to initiate breath Cardiac effects: ↓ preload by ↑ intrathoracic pressure → ↓ venous return; ↓ afterload by ↓ cardiac transmural pressure; may ↑ or ↓ CO and may ↑ or ↓ oxygen delivery

	based on the above Auto-PEEP or intrinsic PEEP (iPEEP): inadeq. exhalation time → lungs unable to completely empty before next breath (ie, "breath-stacking"); if flow ≠ 0 at end-expiration, there must be pressure = auto-PEEP Will ↓ preload and may ↓ CO, espec if hypovolemic Will ↑ work of breathing as must be overcome by Pt to trigger breaths; can prevent Pt from triggering ventilator, extrinsic PEEP helps Measure by occluding expiratory port of vent at end-expiration Resolve by: ↑ exp time, ↓ RR, ↓ V_T, Rx bronchospasm and secretions If iPEEP > set PEEP, minimize iPEEP, then set PEEP to ~80% of iPEEP to ↓ ineffective triggering
Inspiratory time	Normally I:E ratio is ~1:2; however, can alter I time (and consequently flow rate, see later); use in pressure-control mode
Inspiratory flow rates	↑ flow rate → ↓ I time → ↑ E time → ∴ may improve ventilation in obstructive disease, but may affect resp rate and bronchodilation/constriction
Peak inspiratory pressure (PIP)	Dynamic measurement during inspiration; set in pressure-targeted mode Determined by airway resistance and lung/chest wall compliance ↑ PIP w/o ↑ P_{plat} → ↑ airway resist (eg, bronchospasm, plugging) ↓ PIP → ↓ airway resistance or air leak in the system
Plateau pressure (P_{plat})	Static measurement at end of inspiration when no flow; measure via inspiratory hold maneuver on ventilator Determined by resp system compliance (resist. not a factor since no flow) ↑ P_{plat} → ↓ lung or chest wall compliance (eg, PTX, pulmonary edema, pneumonia, atelectasis), ↑ PEEP or auto-PEEP Aim for P_{plat} <30 cm H_2O to ↓ barotrauma (improve by ↓ V_T, ↓ PEEP, ↑ compl [eg, by diuresis])

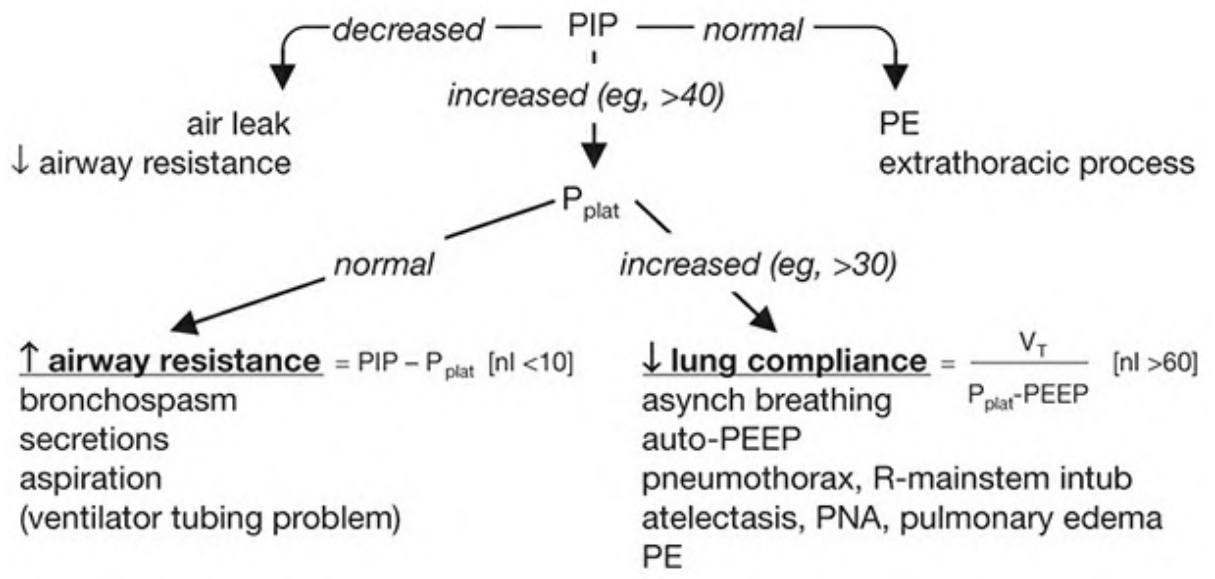
Tailoring the ventilator settings

- To improve oxygenation: options include ↑ F_iO_2, ↑ PEEP
  - S_aO_2 88–92% acceptable, but target mid-90s (*NEJM* 2022;387:1759; *JAMA* 2022;328:1818)
  - First, ↑ F_iO_2. If >0.6 and oxygenation remains suboptimal, then try ↑ PEEP.
  - If ↑ P_aO_2/F_iO_2 *and* P_{plat} stable, suggests recruitable lung (ie, atelectasis). If PEEP 20 & F_iO_2 1.0 and oxygenation remains suboptimal, consider rescue/experimental strategies (see "ARDS").
  - If ↑ PEEP yields no Δ *or* ↓ P_aO_2/F_iO_2 *or* ↑ P_aCO_2, suggests additional lung *not* recruitable and instead overdistending lung → ↑ shunt & dead space; ∴ ↓ PEEP
- To improve ventilation: ↑ V_T or inspiratory pressure, ↑ RR (may need to ↓ I time). Nb, tolerate ↑ P_aCO_2 (permissive hypercapnia) in ALI/ARDS (qv) as long as pH >7.2.

Acute ventilatory deterioration (usually ↑ PIP)

- Response to ↑ PIP: disconnect Pt from vent, bag, auscultate, suction, ✓ CXR & ABG

Figure 2-6 Approach to acute ventilatory deterioration



(Adapted with permission from *Marino's the ICU Book*, 4th ed, 2014.)

Liberating from the ventilator (*NEJM* 2012;367:2233; *Lancet* 2016;387:1856)

- Perform daily assessment of readiness for spontaneous breathing trial (SBT)
- Clinical screening criteria: VS stable, minimal secretions, adequate cough, cause of respiratory failure or previously failed SBT reversed
- Vent parameters: P_aO_2/F_iO_2 >200, PEEP ≤5, f/V_T <105, V_E <12 L/min, VC >10 mL/kg; rapid shallow breathing index (f/V_T) >105 predicts failure, NPV 0.95 (*NEJM* 1991;324:1445)
- Daily awakening trial (d/c all sedation; *Lancet* 2008;371:126): open eyes & w/o: agitation, RR >35, S_aO_2 <88%, resp distress or arrhythmias (if fail, restart sedation at 1⁄2 prior dose)
- SBT = CPAP × 30 min superior to T-piece × 120 min (*JAMA* 2019;321:2175) failure if: deteriorating ABGs, ↑ RR, ↑ or ↓ HR, ↑ or ↓ BP, diaphoresis, anxiety
- Tolerate SBT → extubation. Fail SBT → ? cause → work to correct → retry SBT qd.
- If high risk, extubate to either NIV or NIV alternating w/ HFNC (*JAMA* 2019;322:1465)
- ? acetazolamide in Pts w/ COPD & metabolic alkalosis (*JAMA* 2016;315:480)

Complications

- Oxygen toxicity (theoretical); proportional to duration + degree of ↑ oxygen (F_iO_2 >0.6)
- Ventilator-induced lung injury (see "ARDS")
- Ventilator-associated pneumonia (VAP; ~1%/d, mortality rate ~30%)
  typical pathogens: MRSA, *Pseudomonas*, *Acinetobacter*, and *Enterobacter* species
  preventive strategies: wash hands, HOB elevated, non-nasal intub., enteral nutrition rather than TPN?, routine suction of subglottic secretions, avoid unnecessary abx & transfusions. Inhaled amikacin may ↓ VAP (*NEJM* 2023;389:2052).
- Stress ulcers/GIB: prophylaxis w/ PPI ↓ GIB (*NEJM Evid* 2024;3:EVIDoa2400134)
- Laryngeal edema: for high-risk Pts (traumatic or prolonged [>6 d] intubation, large ET tube, reintubation after unplanned extubation) → ✓ cuff leak test [while cuff deflated, listen for audible leak or see if difference between inspired & expired volumes]. If absent, LR ~4.0 for reintubation and Rx w/ methylprednisolone 20 mg IV q4h starting 12 h pre-extub. → ↓↓ edema and 50% ↓ in reintubation (*Lancet* 2007;369:1003).
- Laryngeal ulceration: consider *tracheostomy* for Pts in whom expect >14 d of mech vent → ↓ duration mech vent, ↓ # ICU days (*BMJ* 2005;330:1243); no benefit to performing at ~1 wk vs. waiting until ~2 wk (*JAMA* 2010;303:1483)

- Malnutrition (for all critically ill Pts): *enteral nutrition* initiated early is safe but not necessary (*JAMA* 2012;307:795), but bolus may ↑ risk of VAP & *C. diff.* (*JPEN* 2002;26:174); no clear benefit to ✓ing gastric residuals (*JAMA* 2013;309:249); permissive enteral underfeeding (~1⁄2 of calculated caloric req) & standard enteral feeding w/ similar outcomes (*NEJM* 2015;372:2398); *parenteral nutrition* should be delayed until after day 8 to ↓ risk of infections, cholestasis, RRT, ventilator days (*NEJM* 2011;365:506)
- Oversedation/delirium: BDZs and polypharmacy are risk factors
  - Propofol: HoTN in ~25%; *propofol infusion syndrome* (PRIS) ? espec w/ high (>5 mg/kg/h) & prolonged (>48 h) infusions & concom vasopressors → ↑ AG, cardiac dysfxn, rhabdomyolysis, ↑ triglycerides, & renal failure (*Crit Care* 2009;13:R169)
  - Dexmedetomidine: no benefit on vent-free days (*JAMA* 2016;315:1460 & 2017;317:1321); similar outcomes to propofol when utilized as sole agent (*NEJM* 2021;384:1424)

ACUTE RESPIRATORY DISTRESS SYNDROME

Global definition (*AJRCCM* 2024;209:37)

- Acute onset within 1 wk of clinical insult or worsening respiratory status
- Bilateral infiltrates without alternative explanation (eg, effusion, atelectasis, nodules)
- Edema not fully explained by fluid overload or congestive heart failure
- Hypoxemia: calculate P_aO_2/F_iO_2 (P:F ratio) or S_pO_2/F_iO_2 (S:F ratio) if $S_pO_2 \leq 97\%$

Type of Ventilation	Mild	Moderate	Severe
PPV (>5 mmHg PEEP)	200 < P:F ≤ 300	100 < P:F ≤ 200	P:F ≤ 100
	235 < S:F ≤ 315	148 < S:F ≤ 235	S:F ≤ 148
NIV/CPAP (PEEP 5) or HFNC	P:F ≤ 300 or S:F ≤ 315 (no gradations endorsed)		

Pathophysiology (*Lancet* 2016;388:2416)

- ↑ intrapulmonary shunt → hypoxemia (∴ Rx w/ PEEP to prevent derecruitment)
- ↑ increased dead space fraction (see "Appendix"), predicts ↑ mort (*NEJM* 2002;346:1281)
- ↓ compliance: $V_T/(P_{plat} - PEEP)$ <50 mL/cm H_2O
- Diffuse alveolar damage (DAD) seen in 40% of autopsies (*AJRCCM* 2013;187:761)

Etiologies	
Direct Injury	**Indirect Injury**
• Pneumonia (~40%) • Aspiration (~15%) • Near drowning • Inhalation injury • Lung contusion	• Sepsis (~25%) • Shock • DIC • Pancreatitis • Trauma/multiple fractures

If no clear inciting event and ILD considered as alt. dx, consider bx.

Treatment (*Lancet* 2022;400:1157, *AJRCCM* 2024;209:24)

- Goals: maintain gas exchange, sustain life, & avoid ventilator-induced lung injury (VILI)
- Consider **steroids** for all Pts (eg, hydrocort 50 mg q6h or dexamethasone 6 mg/d; regimens vary); ↓ mortality in COVID & bacterial PNA (*NEJM* 2021;384:693 & 2023;388:1931)

Mechanisms of VILI	**Ventilator Strategies** (see ARDSnet.org)
Barotrauma/volutrauma: alveolar dist → mech damage	**V_T ≤6 mL/kg, P_{plat} ≤30 & $P_{driving}$ <15 cm H_2O**, tolerate ↑ P_aCO_2 (but keep pH >7.2), ↓ mortality (*NEJM* 2000;342:1301)
Biotrauma → SIRS	Low V_T, open lung strategy w/ high PEEP
Atelectrauma: repetitive alveoli recruit & decruit	**Titrate PEEP to prevent tidal alveolar collapse** See below for options
Hyperoxia: ? injury; worsened V/Q matching	↑ **PEEP** rather than F_iO_2 (keep <0.60) O_2-induced injury only theoretical in humans

The 6 Ps

- **PEEP** (vide infra)
- **Proning:** if P_aO_2/F_iO_2 <150, prone positioning ≥16 h ↓ mort ~50% (*NEJM* 2013;368:2159)
- **Paralysis** (≤48 h): no benefit routinely (*NEJM* 2019;380:1997); consider if Pt-vent dyssynchrony
- **Peeing (fluid balance):** target CVP 4–6 cm H_2O (if nonoliguric & normotensive) → ↑ vent/ICU-free days, but no Δ mortality (*NEJM* 2006;354:2564); PA catheter unproven (*NEJM* 2006;354:2213); consider BNP >200 to trigger diuresis (UOP goal 4.5–9 mL/kg/h × 3 h)
- **Pulm vasodilators:** inhaled NO or prostacyclins ↑ P_aO_2/F_iO_2; no ↓ mort or vent-free days (*BMJ* 2007;334:779)
- **Perfusion (V-V ECMO):** may be useful if refractory (*NEJM* 2018;378:1965)

PEEP titration methods (best method unclear)

- Best PEEP trial: incremental PEEP titration using compliance, O_2, hemodynamics
  If able to ↑ PEEP w/o ↑ P_{plat}, suggests "recruitability"
  ∴ ↑ PEEP if → ↑ S_aO_2 (target ≥88–90%) & P_{plat} ≤30 cm H_2O → ↓ time on vent, better lung mechanics (*JAMA* 2008;299:646), ? ↓ mortality (*JAMA* 2010;303:865)
- ARDSnet "high" PEEP table for optimal F_iO_2/PEEP combo for goal S_aO_2 (ARDSnet.org)
- Recruitment maneuvers: stepwise preferred, routine use not recommended (*Resp Care* 2015;60:1688); recruitment maneuvers at ↑ pressures ? ↑ mortality (*JAMA* 2017;318:1335)
- Esophageal balloon: used to estimate pleural pressure and thereby estimate transpulmonary pressure (ie, true airway distending pressure). Adjusting PEEP according to esoph pressure to maintain optimal transpulm. pressure does not Δ ventilator-free days or mortality, although does ↓ need for advanced rescue Rx (vide supra) (*JAMA* 2019;321:846).
- Driving pressure (ΔP = $P_{plateau}$ − PEEP): ↓ ΔP a/w ↑ survival; target <15 (*NEJM* 2015;372:747)

Prognosis (*JAMA* 2016;315:788)

- Mortality ~40% overall in clinical trials; 9–15% resp. causes, 85–91% extrapulm (MODS)
- Survivors: PFTs ~normal, ↓ D_LCO, muscle wasting, weakness persists (*NEJM* 2003;348:683), ↓ exercise tolerance, ↓ oQl, ↑ psych morbidity (*NEJM* 2011;364:1293); 44% of previously employed Pts jobless at 12 mos (*AJRCCM* 2017;196:1012)

SEPSIS AND SHOCK

Definitions (*JAMA* 2016;315:801; 2017;317:290 & 301; *Crit Care Med* 2021;49(11):e1063)	
Sepsis	Life-threatening organ dysfxn (SOFA ≥2) due to infection Tools incl. SIRS, NEWS, and MEWS to detect early sepsis
Septic shock	Sepsis-induced circulatory and cellular/metabolic abnormalities severe enough to ↑ mortality; hypotension requiring pressors for MAP ≥65 and lactate >2 despite adequate fluid resuscitation
Sequential Organ Failure Assessment (SOFA): ↑ points for worsening organ dysfxn: respiration (↓ P:F ratio); coag (↓ plt); liver (↑ bili); CV (↓ MAP or ↑ pressors); CNS (↓ GCS); renal (↑ Cr or ↓ UOP)	

Shock (see "PA Catheter & Tailored Therapy" for subtypes; *NEJM* 2013;369:1726)

- Tissue hypoxia due to ↓ tissue perfusion and hence ↓ tissue O_2 delivery and/or ↑ O_2 consumption or inadequate O_2 utilization
- Typical signs include HoTN (SBP <90 mmHg or drop in SBP >40 mmHg), tachycardia, oliguria (UOP <0.5 cc/kg/h), Δ mentation, metabolic acidosis ± ↑ lactate
- Hard to dx as ↑ SVR can maintain SBP, but tissue perfusion poor; shock index (HR/SBP) >0.9 and pulse pressure [(SBP − DBP)/SBP] <25% clues to significant shock

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MANAGEMENT (*Crit Care Med* 2021;49:e1063; *NEJM* 2024;391:2133)

Fluids

- Aggressive IV fluid resuscitation (30 mL/kg) admin in boluses w/in 3 h of presentation
- Crystalloid as good as colloid for resuscitation (*JAMA* 2013;310:1809; *NEJM* 2014;370:1412)
- No consistently seen benefit of balanced crystalloid (LR, Plasma-Lyte) vs. NS in terms of mortality, organ failure, or need for RRT (*NEJM* 2018;378:829 & 2022:386:815)
- $NaHCO_3$ may ↓ mortality & need for RRT if AKI & pH <7.2 (*Lancet* 2018;392:31)
- Predictors of fluid responsiveness: pulse pressure variation >13% w/ respiration (*Chest* 2008;133:252); resp. variation in IVC diam, or >10% ↑ in pulse pressure w/ passive leg raise. Static CVP poor surrogate.
- After adequate initial fluid resuscitation, no Δ in outcomes between restrictive fluid strategy (ie, favoring pressors) or liberal strategy (*NEJM* 2022;386:2459 & 2023;388:499)
- After early resuscitation, if ALI/ARDS, target CVP 4–6 mmHg because additional fluids may be harmful → ↑ ventilator/ICU days (*NEJM* 2006;354:2564; *Chest* 2008;133:252)

Pressors & inotropes (also see "ICU Medications")

- MAP target 65 mmHg as good as 80–85 and ↓ AF (*NEJM* 2014;370:1583; *JAMA* 2020;323:938)
- Norepinephrine: ↓ arrhythmia & mortality c/w dopamine (*NEJM* 2010;362:779; *Crit Care Med* 2012;40:725) and ∴ is pressor of choice in septic shock
- Vasopressin: adding to norepi (vs. using high-dose norepi) ↓ risk of AF & RRT by ~¼ (*JAMA* 2018;319:1889)
- If refractory vasoplegia: angiotensin II (*NEJM* 2024;377:419), hydroxocobalamin (*Chest* 2023;163:303) or methylene blue (*J Clin Med* 2022;20:1121), steroids (vide infra)

Targets

- Lactate clearance (≥20%/2 h) as effective as $S_{cv}O_2$ to guide resusc. (*JAMA* 2010;303:739)
- Targeting capillary refill time ≤3 sec (check q30min) as good if not better than lactate clearance (*JAMA* 2019;321:654)

Antibiotics

- Start empiric IV abx as soon as possible after recognition of severe sepsis or septic shock; every

hr delay in abx admin a/w 7.6% ↑ in mortality (*Crit Care Med* 2006;34:1589), abx admin w/in 3 h of presentation in the ED a/w ↓ in-hospital mortality (*NEJM* 2017;376:2235)
- If possible, obtain 2 sets of BCx before urgently starting abx (but do not delay abx)
- Broad gram-positive (incl MRSA) & gram-neg (incl highly resistant) coverage, ± anaerobes
- Impact of procalcitonin-guided cessation on mort. unclear (*CCM* 2018;46:684; *JAMA* 2024;333:682)
- Empiric micafungin in critically ill Pts w/ *Candida* colonization & sepsis of unknown etiology ↓ invasive fungal infxns & tended ↑ invasive fungal infxn-free survival, espec. in Pts w/ 1,3-β-D-glucan >80 (*JAMA* 2016;316:1555)

Steroids (*Crit Care Med* 2018;46:1411)

- Hydrocortisone 50 mg IV q6 + fludrocortisone 50 µg via NGT daily in septic shock ↓ duration of shock by ~1 d and may ↓ mortality (*NEJM* 2018; 378:797 & 809)
- Consider in Pts w/ refractory shock on escalating doses of pressors

Early Goal-Directed Therapy (EGDT)

- Historically: IVF & pressors for MAP ≥65 mmHg, CVP 8–12 mmHg, UOP ≥0.5 mL/kg/h; inotropes & PRBCs for $S_{cv}O_2$ ≥70% in 6 h (*NEJM* 2001;345:1368)
- However, now in era of early abx and adequate fluid resuscitation, no ↓ in mortality w/ EGDT vs. current usual care, and ↑ hospital costs (*NEJM* 2017; 376:2223)

TOXICOLOGY

Drug/Toxin	Signs/Sx and Diagnostics	Management Options
Acetaminophen	Vomiting, ↑ AG & nl OG metabolic acidosis, hepatitis & hepatic failure, renal failure	N-acetylcysteine (NAC) infusion Hemodialysis if massive O/D See "Acute Liver Failure"
Salicylates	Tinnitus, hyperventilation, abd. pain, vomiting, ΔMS, mixed ↑ AG & nl OG metabolic acidosis + respiratory alkalosis	IVF resuscitation Alkalinization w/ $NaHCO_3$ Maintain respiratory alkalemia Consider hemodialysis
Opioids	↓ mentation, ↓ RR, miosis	IV naloxone
Benzodiazepines	↓ mentation, ataxia, ↓ RR	Flumazenil *not* rec (can precipitate withdrawal/seizures)
Calcium channel blockers	Bradycardia, AV block, hypotension, HF, hyperglycemia	IVF, vasopressors, Ca infusion, hyperinsulinemic euglycemia, ? intralipid emulsion, pacing
α **Blockers**	Bradycardia, AV block, hypotension, HF, hypoglycemia	Glucagon, vasopressors, pacing
Digoxin	N/V, bradycardia, AV block, delirium, xanthopsia ✓ serum dig level (but may be inaccurate if <6 h since last dose), renal function	Correct hypokalemia Digibind if hyperkalemia, life-threatening dysrhythmia Consider hemodialysis Lidocaine for arrhythmias
Tricyclic antidepressants	Hypotension, seizures, arrhythmia, ↑ QRS, ↑ QT	IVF resuscitation, IV sodium bicarbonate, vasopressors

Lithium	N/V/D, tremor, hyperreflexia, clonus, drowsiness, seizure, ↑ QT, AV block, bradycardia	IVF (NS), maintain UOP Consider hemodialysis
Ethylene glycol	CNS depression, ↑ AG & OG metabolic acidosis	Ethanol or fomepizole, $NaHCO_3$ Consider hemodialysis
Methanol (*NEJM* 2018;378:270)	CNS depression, blindness ↑ AG & OG met. acidosis	Ethanol or fomepizole, $NaHCO_3$ Consider hemodialysis
Isopropanol	CNS depression, gastritis	Supportive care
Carbon monoxide	HA, dizziness, nausea, ΔMS carboxyHb level, CO-oximetry	100% normobaric oxygen, hyperbaric O_2 in severe cases
Organophos-phate	Salivation, lacrimation, diaphoresis, miosis, emesis, bronchospasm, ΔMS	Endotracheal intubation for respiratory failure, atropine, pralidoxime, benzodiazepines
Cyanide	Coma, seizure, metabolic acidosis, hypotension	IV Na nitrite and Na thiosulfate IV hydroxocobalamin

Call local Poison Control for assistance with management (*Chest* 2011;140:1072)

LUNG TRANSPLANT

Overview (*NEJM* 2024;391:1822)

- Indications: end stage, progressive decline despite max medical Rx, <2-y life expectancy due to lung disease; COPD, ILD (IPF), pulmonary HTN, cystic fibrosis, α-1-antitrypsin
- Relative contraindic: age >70, uncontrolled/unRx'd infxn, malig in prior 5 yrs, severe non-pulm dis., BMI ≥35 or <16, active smoking, EtOH/drug depend., med nonadherence, psychosocial

Posttransplant care

- Immunosuppression: no single best regimen. Calcineurin inhibitor (tacro > cyclosporine, ↓ incidence of graft failure (*JHLT* 2021;40:S165)) + steroids + MMF or AZA.
- Monitoring: clinic visits, serial PFTs, chest X-ray, bronchoscopy w/ transbronchial biopsy

Complications

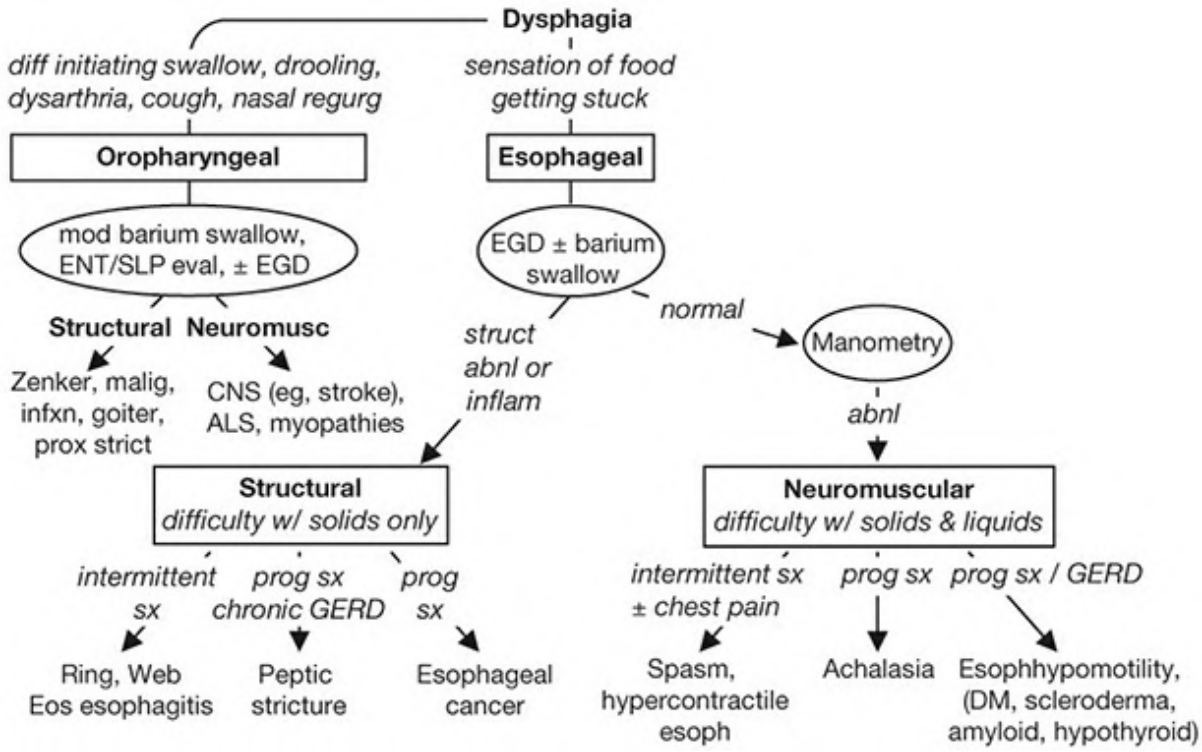
- Primary graft dysfunction (PGD): acute lung injury following txp; assoc w/ early mortality
- Anastomotic: vascular (stenosis, thrombosis) and airway (infection, necrosis, dehiscence, granulation tissue, tracheobronchomalacia, stenosis, fistula)
- Acute rejection: ↓ lung fxn, cough, SOB, fever; Dx w/ trans-bronch bx; Rx immunosupp
- Chronic rejection: bronchiolitis obliterans w/ obstruction; Dx w/ PFTs, trans-bronch bx; Rx limited (azithromycin, montelukast, Δ immunosuppressives)
- Infection: ↑ bacterial, fungal, viral pneumonia, systemic infections, CMV, OI
- Malignancy: 2× ↑ risk overall. 5.5× ↑ risk lung cancer. PTLD (assoc w/ EBV) common.
- Misc: GVHD, CKD, DM, CAD, CHF, stroke, encephalopathy, drug toxicity

ESOPHAGEAL AND GASTRIC DISORDERS

Dysphagia

- Oropharyngeal: inability to propel food from mouth through UES into esophagus
- Esophageal: difficulty swallowing & passing food from esophagus into stomach

Figure 3-1 Etiologies of and approach to dysphagia (*Am J Med* 2015;128:1138.e17-23)



Structural dysphagia (solids > liquids; *JAMA* 2015;313:18; *Gastro* 2018;155:1022)

- **Oropharyngeal**
  - Zenker divertic. (pharyngeal pouch): in elderly, a/w aspir., dx w/ video fluoro; Rx endo/surg
  - Malignancy; proximal strictures/rings/webs; infection; radiation injury; goiter; osteophytes
- **Esophageal**
  - Rings (intermittent dysphagia, concentric obstructing tissue, Schatzki ring): near GE jxn, a/w food impaction, linked to GERD. Rx w/ PPI, dilation.
  - Webs: thin, partially occlusive structure, proximal, a/w Fe defic. (Plummer–Vinson synd.)
  - Peptic or XRT strictures, foreign body, tumor, vascular rings (dysphagia lusoria), compression from dilated left atrium compression
  - Infxn esophagitis: odynophagia > dysphagia; often immunosupp w/ *Candida*, HSV, CMV
  - Pill esophagitis: odynophagia > dysphagia; NSAID, KCl, bisphosp., doxy & tetracycline
  - Eosinophilic esophagitis (*JAMA* 2021;326:1310; *Am J Gastro* 2025;120:31): often young/middle-aged ♂.
    Dx: >15 eos/hpf on bx, esoph dysfxn (ie, dysphagia, food impaction). Rx: 1st line is PPI (1/2

respond); alternative (or if fail PPI) is **3Ds**: 1st elimination **D**iet (⌀ milk, soy, eggs, wheat, nuts, fish); if no Δ, **D**rugs (swallow inh steroids, consider dupilumab [*NEJM* 2022;387:2317]); if ongoing sx & stricturing, **D**ilation (*Gastro* 2020;158:1776).

Neuromuscular dysphagia (solids & liquids; *Neurogastro Motil* 2021;33:e14058)

- Caused by aberrant motility or innervation of oropharynx/esophagus
- Oropharyngeal: consider CNS disorders (eg, stroke, ALS, myopathies, CNS tumors)
- Esophageal: motility disorder w/ dysphagia, chest pain, GERD; dx: high-res manometry w/ esophageal pressure topography. Chicago classification v4.0:
  1. Disorders of EGJ Outflow: *Isolated EGJ outflow obstruction or achalasia. Achalasia:* simult. ↓ amp contract. & ↓ LES relaxation; barium swallow w/ dilated esophagus & distal "bird's beak" narrowing; mostly idiopathic, although a/w Chagas; Rx: pneumatic dilation as effective as Hel myotomy (local expertise dependent); peroral endoscopic myotomy; CCB/nitrates/PDEi; boto surg cand.
  2. Disorders of Peristalsis: *Absent contractility* (failed peristalsis); *distal esophageal spasm* (unc peristalsis w/ simult. contract.); *hypercontractile esoph* (high amp contract.; Rx w/PPI, nitrates/CCB/PDEi, TCA); *ineffective esophageal motility* (↓ amp of distal esoph contract.; see scleroderma, DM, hypothyroid.; Rx underlying disorder & w/ PPI)

Gastroesophageal Reflux Disease (GERD)

Pathophysiology (*NEJM* 2022;387:1207)

- ↑ acid exposure in esophagus, caused by ↑ transient LES relaxations. Worsened by ↑ intra-abd pressure (eg, obesity, preg.), ↓ esophagogastric motility, hiatal hernia. Rarely caused by ↑ secretory states (eg, Zollinger–Ellison).
- Precipitants: supine, fatty foods, caffeine, alcohol, cigarettes, CCB, pregnancy, obesity

Clinical manifestations

- Esophageal: **heartburn**, atypical chest pain, regurgitation, sour taste, dysphagia
- Extraesophageal: **dry cough**, asthma (often poorly controlled), laryngitis, dental erosions

Diagnosis (*Annals* 2015;163:ITC1; *Nat Rev Gastro Hepatol* 2016;13:501)

- Clinical diagnosis based on sx and response to empiric trial of PPI ("PPI test")
- EGD if: ⌀ response to PPI or *alarm features*: dysphagia, vomiting, ↓ wt, anemia, age >60
- If dx uncertain & EGD nl → esoph manometry w/ 24-h pH monitoring ± impedance to dx:
  "Nonerosive reflux disease": no erosion, ulceration, or Barrett's; 1⁄2 abnl pH. Unpredictable response to PPI. Most will *not* progress to erosive esophagitis or Barrett's.
  "Reflux hypersensitivity": nl acid exposure on pH/impedance w/ reflux-assoc. sx
  "Functional heartburn": nl acid exposure on pH/impedance w/o reflux-assoc. sx

Treatment (*World J Gastrointest Endosc* 2018;10:175; *Am J Gastro* 2022;117:27; *CGH* 2024;22:2215)

- Lifestyle: avoid precipitants, lose weight, no eating 2 hrs before bed, exercise, ⌀ tobacco
- Medical: start low-dose PPI, uptitrate up to 40 mg bid; H2 blockers for intermittent sx
- Refractory (max dose ≥8 wks): confirm w/ pH testing on or off PPI, consider hernia repair
  Acidic or sx correlate w/ reflux: consider vonoprazan for severe/refractory erosive and nonerosive GERD. Endoscopic or surgical options: fundoplication; LES sphincter augmentation w/ radiofrequency, implantable magnetic or electrical devices.
  If nl pH or no sx correlation = "fxnal dyspepsia"; Rx w/ TCA, SSRI, SNRI, trazodone

Complications (*Gastro* 2020;158:760; *JAMA* 2022;328:663)

- Reflux esophagitis (erosions/ulcers above GE jxn), strictures (caused by chronic inflamm)
- Barrett esoph. (BE): metaplastic columnar mucosa above GE jxn replaces squam epithel.
  Screen if chronic (>5 y) and/or frequent GERD (≥1/wk) in ♂ w/ ≥3 risk factors for Barrett or esoph. adeno: >50 y, White, obesity, smoking, FHx of Barrett's or esophageal adeno. In ♀, consider only if multiple RFs. 0.1–0.3%/y risk of esoph adenocarcinoma, ↑ if ↑ dysplasia (*Am J Gastro* 2016;111:30).
  Mgmt: PPI. W/o dysplasia: EGD q3–5y. Low-grade dysplasia: repeat EGD at 6 & 12 mo and then q12mo; possible endoscopic eradication. High-grade dysplasia: endoscopic eradication; consider chemoprophylaxis w/ high-dose PPI & ASA (*ACG* 2022;117:559).

Peptic Ulcer Disease (PUD)

Definition & etiologies (*Lancet* 2024;404:68; *JAMA* 2024;332:1832)

- Ulcers (break in mucosal lining >5 mm) & erosions (<5 mm) in stomach and duodenum
- Principal risk factors: *H. pylori* infection > ASA/NSAID use
- ***H. pylori* infection:** causes ~80% of duodenal ulcers (DU) & ~30–40% of gastric ulcers (GU). ~50% of world colonized w/ *H. pylori*, but only 10–15% will develop PUD.
- **ASA/NSAIDs:** damage to mucosa caused by ↓ prostaglandin synthesis. Cause majority of non–*H. pylori*-related DU & GU. Regular use a/w 5–6× ↑ odds of GIB.
- Other risk factors/causes: smoking, excessive EtOH, gastric cancer/lymphoma, Crohn's, viral infxn (eg, CMV/HSV in immunosupp), bisphosphonates, steroids (in combo w/ NSAIDs); rarely gastrinoma (Zollinger–Ellison synd.), mastocytosis, idiopathic
- Stress ulcer: risk factors = ICU & coagulopathic, mech vent, h/o GIB, steroid use; Rx w/ PPI

Clinical manifestations

- **Epigastric gnawing abdominal pain:** relieved with food (DU) or worsened by food (GU)
- Complic.: UGIB, perf. & penetration, gastric outlet obstruction (due to edema & dysmotility)

Diagnostic studies

- Testing for *H. pylori:* stool Ag, urea breath testing (UBT) or EGD + rapid urease test (RUT) False ⊖ Ag, UBT, RUT if on abx, bismuth, PPI; ∴ stop prior to testing if possible Serology: ↓ utility, useful only to exclude infection in lower prevalence areas
- EGD (definitive dx): if fail empiric Rx or alarm features (see "GERD"); bx GU to r/o malig & *H. pylori;* repeat EGD in 6–12 wk if >2 cm, malig features, risk factors for gastric cancer (ie, ⊕ FHx, ⊕ *H. pylori*, atrophic gastritis, metaplasia on bx, >50 y), or sx persist

Treatment (*AJG* 2024;119:1737)

- **If *H. pylori*** ⊕ → **eradicate** ("test and treat"); if ⊖ → gastric acid suppression w/ PPI
  1st line: Quad. Rx: 14d × [MNZ + TCN + bismuth + PPI] or combo pill: Pylera or Helidac
  Besides PUD, test & Rx if: gastric MALT lymphoma, s/p resection for early gastric ca, FHx gastric ca, unexplained iron def. anemia, ITP, uninvestigated dyspepsia in Pt <60 y, or when initiating long-term NSAIDs
- "Test-of-cure": 4 wk after Rx, off PPI × 1–2 wk. Use stool Ag, EGD + RUT, or UBT.
- Lifestyle changes: d/c smoking and probably EtOH; diet does not seem to play a role
- Surgery: if refractory to med Rx (1st r/o NSAID use) or for complic. (vide supra)

GI prophylaxis if taking ASA/NSAID (*Am J Gastro* 2009;104:728)

- PPI if h/o PUD/UGIB and either (a) on $P2Y_{12}$ inhib or anticoag, or (b) ≥2 of the following: >60 y, steroids, dyspepsia. Low bleeding risk Pts unlikely to benefit (*Gastro* 2019;157:403).
- Consider Δ nonselective NSAID to selective COX-2 inhibitor (↓ PUD & UGIB but ↑ CV events), if

low CV risk & not on ASA

GASTROINTESTINAL BLEEDING

Definition

- Intraluminal blood loss anywhere from the oropharynx to the anus
- Classification: **upper** = above the ligament of Treitz; **lower** = below the ligament of Treitz
- "Severe" GIB: defined as having associated shock, orthostatic hypotension, ↓ Hct by 6% (or ↓ Hb by 2 g/dL), or requiring transfusion ≥2 U PRBCs. Requires hospitalization.

Clinical manifestations

- **Hematemesis** = blood in vomitus (UGIB)
- **Coffee-ground emesis** = emesis of blood exposed to gastric acid (UGIB)
- **Melena** = black, tarry stools from digested blood (usually UGIB, but can be SB or R colon)
- **Hematochezia** = bloody or maroon-colored stools (LGIB or rapid UGIB)

Initial management (*Am J Gastro* 2023;118:208)

- **Assess severity:** *VS including orthostatic* Δ*s, JVP.* Tachycardia (can be masked by βB use) suggests 10% volume loss, orthostatic hypotension 20% loss, shock >30% loss. Scoring predicts rebleeding & mortality: Glasgow–Blatchford, AIMS65, ABC, Oakland.
- **History:** prior GIB, tempo of current bleed, specific bleeding manifestations (see above), other GI s/s (eg, abd pain, Δ in bowel habits, wt loss, N/V), ASA/NSAID or EtOH use, anticoag/antiplt drugs, h/o or risk factors for cirrhosis, radiation, prior GI or aortic surgery
- **Physical exam:** localizable abd tenderness, peritoneal signs, masses, LAN, prior surgery, signs of liver disease (hepatosplenomegaly, ascites, jaundice, telangiectasias), rectal exam: masses, hemorrhoids, anal fissures, stool appearance, color
- **Resuscitation:** placement of 2 large-bore (18-gauge or larger) intravenous lines.
- Volume replacement: NS or LR to achieve normal VS, UOP, & mental status.
- **Lab studies: Hct** (*may be normal* in first 24 h of acute GIB before equilibration) 2–3% → 500 mL blood loss; low MCV → Fe defic. and chronic blood loss; **plt**, **PT/INR**, **PTT**; BUN/Cr (ratio >36 in UGIB b/c GI resorption of blood ± prerenal azotemia); LFTs
- **Transfuse:** type & cross; use O-neg if emerg; for UGIB (esp. w/ portal HTN) transfuse w/ more restrictive Hb goal (eg, >7 g/dL or >8 g/dL if CAD) (*JAMA* 2016;316:2025)
- **Reverse coagulopathy:** consider PCC or FFP to normalize INR if life-threatening GIB or INR substantially elevated (however caution in ESLD as INR does not correlate w/ bleeding); plts >50k, ddAVP if uremic, consider reversal agents if on anticoag. (qv)
- **Triage:** alert endoscopist. Consider ICU if unstable VS or poor end-organ perfusion. Intubation for: emergent EGD, ongoing hematemesis, shock, poor resp status, Δ MS. OutPt management if SBP ≥110, HR <100, Hb ≥13 (♂) or ≥12 (♀), BUN <18, ∅ melena, syncope, heart failure, liver disease (*Clin Gastro Hepatol* 2015;13:115).

Diagnostic studies (*JACR* 2021;18:S139; *Am J Gastro* 2023;118:208 & 2024;119:438)

- UGIB: **EGD** w/in 24 h (*NEJM* 2020;382:1299). If severe bleed, ↑ dx/Rx yield if **erythro 250 mg IV given 30 min prior to endoscopy** to clear stomach contents.
- LGIB: **colonoscopy** (identifies cause in >70%); non-emergent colo (after 24 h) as urgent (w/ in 24 h) not been shown to improve outcomes. If hematochezia a/w orthostasis, concern for brisk UGIB → *exclude UGIB w/ EGD first.* Colo may not be needed if bleeding subsides and Pt received high-quality colo in past 12 mo. **CTA** if ongoing hematochezia or too unstable for colo &

hemodyn. unstable (*Am J Gastro* 2023;118:208)

- If ⊕ CTA or too unstable for endo and ongoing bleeding, consider arteriography & IR embolization or surgery. Colo can be considered after ⊕ CTA.
- Emergent exploratory laparotomy (last resort) if no localization and life-threatening bleed

Etiology UGIB	Comment & Treatment (*Dig Dis Sci* 2018;63:1286)
PUD (20–60%; duodenal > gastric) (*Am J Gastro* 2021;116:899) See "PUD"	*Treatment:* **PPI:** 40 mg PO or IV BID **Endoscopic therapy:** epi inj + bipolar cautery or hemoclip. Bx for *H. pylori* and treat if ⊕. *High-risk (for rebleeding) ulcer*: arterial spurting, adherent clot, visible vessel. Endo Rx, IV PPI × 72 h post-EGD, then Δ to high-dose oral PPI. If fail, arteriography w/ embolization; surgery (last resort). *Intermediate-risk ulcer*: oozing, in o/w stable Pt. Endo Rx, can Δ to oral PPI after EGD and observe 24–48 h. *Low-risk ulcer:* clean-based or flat. Oral PPI & discharge. Hold anticoag & antiplatelet Rx until hemostasis; can resume after hemostasis & PPI on board
Erosive gastropathy (4–30%)	Precipitants: ASA/NSAID, EtOH, cocaine, gut ischemia, XRT Stress-related mucosal injury in ICU Pts. Risk factors include severe coagulopathy, mech vent >48 h, high-dose steroids. Treatment: high-dose PPI

Esophagitis (15%)		Rx offending cause + high-dose PPI; repeat EGD to r/o Barrett's
Esophageal or gastric varices (4–20%) (*Clin Gastro Hepatol* 2015;13:2109; *J Gastro Hepatol* 2016;31:1519; *Hep* 2017;65:310; *Hep* 2024;79:1194) See "Cirrhosis"		2° to portal HTN. If isolated gastric → r/o splenic vein thrombosis. <u>*Pharmacologic*</u> Start **octreotide** pending EGD if suspect varices: Rx for 2–5 d Abx: 20% cirrhotics p/w GIB have infxn, & ~50% develop infxn during hospitalization; Ppx w/ IV CTX, cipro, or levoflox × 5 d <u>*Nonpharmacologic*</u> Esophageal varices: **endoscopic band ligation** (>90% success). Covered esophageal stent placement or balloon tamponade if refractory as bridge to TIPS (consider early espec. if Child–Pugh C). Gastric varices: arteriography w/ coiling, or if available, endoscopic injection of cyanoacrylate (glue). If refractory: TIPS or balloon-retrograde transvenous obliteration (BRTO).
Portal HTN gastropathy		↑ portal venous pressure → ectatic vessels, hyperemia in gastric antrum. Rx: reduce portal HTN (octreotide), βB, TIPS.
Vascular (5–10%)	Angioectasia AVMs, HHT (vide infra)	AVMs congenital. Angioectasia (ectatic submucosal vessels) a/w ↑ age, CKD, cirrhosis, CTD, severe CV dis. *Heyde syndrome:* GIB due to angioectasias + AS. Rx: endoscopic; thalidomide (*NEJM* 2023;389:1649) or long-acting octreotide for SI angioectasia.
	Dieulafoy lesion	Enlarged (1–3 mm) submucosal artery protruding through fundal mucosa → sudden, massive UGIB. *Difficult to identify.* Endo Rx.
	Gastric antral vasc. ectasia (GAVE)	"*Watermelon stomach*"; ectatic gastric vessels, often a/w cirrhosis, CTD, typically older ♂. Rx w/ EGD w/ thermal hemostasis, repeat q4–8wk to eradicate lesions. TIPS does *not* improve outcomes.
	Aortoenteric fistula	AAA or aortic graft erodes into 3rd portion of duodenum. P/w "herald bleed." If low suspicion → endoscopy; if high → CT angiography.

Malignancy (5%)	Endoscopic hemostasis of mass (occasionally XRT) temporizing measure till cancer Rx
Mallory–Weiss tear (5–10%)	GE jxn lacerations due to vomiting → ↑ intra-abd pressure & shearing Often self-resolve; Rx→ antiemetics, PPI, endoscopic therapy
Cameron lesions	Linear erosions in hiatal hernia due to mech trauma of diaphragm
Post-sphincter- otomy bleeding	Occurs in ~2% of ERCP w/ sphincterotomy; ↑ risk w/ more complic. procedure. Bleeding into duodenum. Rx w/ endo hemostasis.

Etiology LGIB	**Comment & Treatment** (*NEJM* 2017;376:1054; *Am J Gastro* 2023;118:211)
Diverticular bleed (30%)	*Pathophysiology:* intimal thickening and medial thinning of vasa recta as they course over dome of diverticulum → weakening of vascular wall → arterial rupture. Diverticula more common in left colon; but *bleeding diverticula more often in right colon.* *Clinical:* older, ASA/NSAIDs, usually painless hematochezia ± abd cramping *Treatment:* usually stops spontaneously (~75%); ~20% recur. CTA vs. nonurgent endo hemostasis. Surgery (partial colectomy) last resort.
Polyp/Tumor (20%)	Typically slow ooze, p/w fatigue, weight loss, iron deficiency anemia
Colitis (20%)	Infectious (see "Acute Diarrhea"), IBD, ischemic colitis, XRT
Anorectal disorders (20%)	Internal, external hemorrhoids; anal fissures, rectal ulcers, rectal varices (Rx by ↓ portal venous pressure in cirrhosis), XRT
Vascular (<10%)	Angioectasia & AVMs. *Hereditary hemorrhagic telangiectasia* (Weber–Osler–Rendu): diffuse AVMs throughout GI mucosa (also involve lips, oral mucosa, fingertips).
Meckel diverticulum	Congenital intestinal pouch due to incomplete obliteration of vitelline duct. 2% of pop, w/in 2′ of IC valve, 2″ long, ♂:♀ 2:1, can present as obscure GIB in adults. Dx w/ ^{99m}Tc-pertechnetate scintigraphy. Rx w/ angioembo, surgical resection.

Obscure GIB (*Am J Gastro* 2024;10:1265; *Gastro* 2017;152:497)

- **Definition:** continued bleeding (melena, hematochezia) despite ⊖ EGD & colo; 5% of GIB
- **Etiologies:** Dieulafoy lesion, GAVE, small bowel angiodysplasia, ulcer or cancer, Crohn's disease, aortoenteric fistula, Meckel diverticulum, hemobilia
- **Diagnosis:** repeat EGD w/ push enteroscopy/colonoscopy when bleeding is active
  If ⊖, video capsule to evaluate small intestine (contraindic. if stricture)
  If still ⊖, consider enteroscopy (single- or double-balloon, or spiral), CT or MR enterography, CTA, arteriography, ^{99m}Tc-pertechnetate scan ("Meckel scan"), or tagged RBC scan

DIARRHEA

Acute Diarrhea (<4 WEEKS' DURATION)

Acute Infectious Etiologies (*Am J Gastro* 2016;111:602; *JAMA* 2019;321:891)		
NONINFLAMMATORY		**Predom. disruption small intestine absorp. & secretion.** **Voluminous diarrhea, N/V. ⊖ Fecal WBC & FOB.**
Preformed toxin		"Food poisoning," <24 h dur. *S. aureus* (meats & dairy), *B. cereus* (fried rice), *C. perfringens* (rewarmed meats).
Viral (*Lancet* 2018; 392:175)	Rotavirus	Outbreak person to person (PTP), daycare; lasts 4–8 d
	Norovirus	~50% of all diarrhea. Winter outbreaks; PTP & food/water; no immunity. Lasts 1–3 d. Vomiting prominent.
Bacterial	*E. coli* (toxigenic)	>50% of traveler's diarrhea; cholera-like toxin; <7 d
	Vibrio cholerae	Contam H_2O, shellfish; "rice water" stools w/ dehydration
Parasitic (± malab for mos after Rx)	*Giardia*	Streams/outdoor sports, travel, outbreaks. Bloating. Acute (profuse, watery) → chronic (greasy, malodorous).
	Cryptosporidium	In soil; water-borne outbreak; usually self-limited, can → chronic infxn if immunosupp. Abd pain (80%), fever (40%).
	Cyclospora	Contaminated produce, intl travel (Latin America)
INFLAMMATORY		**Predom. colonic invasion. Small-vol diarrhea. LLQ cramps, tenesmus, fever, typically ⊕ fecal WBC or FOB.**
Bacterial	*Campylobacter*	Undercooked poultry, unpasteurized milk; carried by puppies & kittens. Prodrome w/ abd pain, "pseudoappendicitis"; c/b GBS, reactive arthritis.
	Salmonella (nontyphoidal)	Eggs, poultry, milk, hamsters. Bacteremia in 5–10%. 10–33% of bacteremic Pts >50 y may develop aortitis.
	Shigella	Abrupt onset; no N/V; gross blood & pus in stool; ↑↑ WBC
	E. coli (O157:H7 & inv/hemorrhagic non-O157:H7)	Undercooked beef, unpasteurized milk, raw produce; PTP. O157 & non-O157 sp. (40%) produce *Shiga* toxin → HUS (typically in children). Gross blood in stool.
	C. difficile	Vide infra
	Vibrio parahaem.	Undercooked seafood
	Salmonella typhi	Travel to Asia, Africa, S. America. Systemic toxicity, relative brady., rose spot rash, ileus → "pea-soup" diarrhea, bacteremia.
	Other	*Yersinia:* undercooked pork; unpasteurized milk, abd pain → "pseudoappendicitis" (aka mesenteric adenitis) *Aeromonas, Plesiomonas, Listeria* (meats & cheeses)
Parasitic	*E. histolytica*	Contaminated food/water, travel (rare in U.S.); liver abscess
Viral	CMV	Immunosuppressed; dx by shell vial cx of colon bx

Evaluation (*NEJM* 2014;370:1532; *Digestion* 2017;95:293; *PLoS One* 2017;12:11)

- **Ddx:** hyperthyroid, adrenal insufficiency, meds (abx, antacids, ICI), appendicitis, diverticulitis, radiation, 1st presentation of chronic bowel disorder (eg, IBD, celiac)
- **History:** stool freq, blood, abd pain, duration of sxs [~1 wk for viral & bacterial (except *C. diff*), >1 wk for parasitic], travel, food, recent abx, immunocompromised
- **PEx:** vol depletion (VS, UOP, axillae, skin turgor, MS), fever, abd tenderness, ileus, rash
- **Laboratory:** fecal calprotectin, stool cx, BCx, lytes, *C. diff* (if recent hosp/abx), stool O&P (if >10 d, travel to endemic area, exposure to unpurified H_2O, community outbreak, daycare, HIV ⊕ or MSM); ± stool ELISAs (viruses, *Crypto*, *Giardia*), serologies (*E. histolytica*); PCR BioFire GI Panel tests 22 organisms (but high ⊕ rate & unclear if true vs. colonized; consider if immunocompromised)
- **Imaging/endoscopy:** consider if ***warning signs (WS)*** of fever, severe abd pain, blood or pus in stool, >6 stools/d, severe dehydration, immunosupp, elderly, duration >7 d, hosp-acquired. CT/KUB if ? toxic megacolon; sig/colo if immunosupp or cx ⊖.

Treatment (*Am J Gastro* 2016;111:602; *Clin Infect Dis* 2017;65:e45)

- If no WS, nl PO intake → supportive: hydrate, loperamide, bismuth subsalicylate (⌀ antichol)
- If mod. dehydration: 50–200 mL/kg/d of oral solution or Gatorade, etc.
- If severe: IV fluids
- If suspect traveler's diarrhea → azithro 1 g × 1 d (due to FQ resistance in Asia), rifaximin, or rifamycin; if suspect protozoal → MNZ or nitazoxanide
- *Empiric* abx for non–*C. diff inflammatory* diarrhea reasonable for severe disease (fever, >6 BMs/d, hospitalized, bloody or mucoid stools or high-risk Pt [> 70 yrs, immunosupp]): azithro 1 g × 1 d (preferred if fever or dysentery) or FQ × 3–5 d (↑ resistance)
- *Avoid* abx if suspect *E. coli* O157:H7 (exposure hx, gross blood) as may ↑ risk of HUS

Clostridioides Difficile Infection (CDI)

Pathogenesis & epidemiology (*NEJM* 2015;372:825)

- Ingestion of *C. diff* spores → colonization when colonic flora Δ'd by abx or chemo → release of toxin A/B → colonic mucosal necrosis & inflammation → pseudomembrane
- Most frequently reported nosocomial infxn; community-acquired w/o abx ~1⁄3 of new cases. A/w *any* abx during or up to 10 wks post Rx (esp. β-lactams, clinda, FQ).
- Elderly, immunocompromised, and IBD Pts can develop CDI w/o recent abx exposure

Clinical manifestations (a spectrum of disease)

- Asx colonization: <3% healthy adults; ~20% in hospitalized patients on antibiotics
- Acute watery diarrhea (>3 stool/d), occ bloody ± mucus, lower abd pain, fever, ↑↑↑ WBC
- Pseudomembranous colitis: above sx + pseudomembranes + bowel wall thickening
- Fulminant colitis (2–3%): **toxic megacolon** (colonic atony/absence of BMs, colon dilatation ≥6 cm on KUB, systemic toxicity) and/or bowel perforation

Diagnosis (*Ann Intern Med* 2018;169:49)

- Only test if *symptomatic* (diarrhea, s/s of colitis); test *liquid* stool (unless concern for ileus)
- **Stool toxin immunoassay** (high Sp) + **glutamate dehydrogenase** (GDH) (high Se)
- **Stool PCR:** has ↑ Se, but ⊕ if colonized in absence of active infxn; should not necessarily Rx if ⊕ PCR w/ neg toxin assay unless clinical picture suggestive (*JAMA IM* 2015;175:1792)
- Classified as nonsevere (WBC <15k, SCr <1.5), severe (>10 BM/d, WBC >15k, SCr >1.5), and fulminant (hypotension/ICU care, ileus, megacolon) CDI
- Obtain CT abdomen/pelvis if suspect complication (toxic megacolon). Consider flex sig if dx uncertain and/or evidence of no improvement on standard Rx.

Initial treatment (*CID* 2021;73:5; *Am J Gastro* 2021;116:1124)

- If possible, d/c abx ASAP; stop antimotility agents & cholestyramine if using (binds vanco)
- Fidaxomicin is now preferred over vancomycin regardless of severity; may be limited by $
- **Nonsevere or severe:** fidaxomicin 200 mg bid (↓ recurrence rate) or vanco 125 mg PO qid × 10 d
- **Fulminant**: vanco 500 mg PO qid + MNZ 500 mg IV q8h; consider vanco PR as well; consider FMT. Fidaxomicin not yet studied in fulminant disease.
- If **worsening** (ileus, ↑ WBC, ↑ lactate, shock, toxic megacolon, peritonitis): abd CT & urgent surgical consult (subtotal colectomy, diverting loop ileostomy, or colonic lavage)
- If need for other abx, cont *C. diff.* Rx for ≥7 d post-abx cessation (*Am J Gastro* 2016;111:1834)
- Stool carriage 3–6 wk postcessation; retesting for *C. diff* as "test of cure" not recommended

Recurrent infection (15–30% risk after d/c of abx, most w/in 2 wk of stopping abx)

- 1st recurrence: fidaxomicin 200 mg PO bid × 10 d or vanco 125 mg PO q6h × 10–14 d. Consider adding bezlotoxumab 10 mg/kg IV × 1 during abx Rx (mAb that binds toxin B), which ↓ recurrence; caution in CHF (*NEJM* 2017;376:305).
- Subsequent recurrences: fidaxomicin or vanco PO pulse → taper. Consult ID. Fecal microbial transplant (*JAMA* 2017;318:1985) recommended after CDI × 3.
- Prevention: vanco 125 mg PO QD ↓ risk of recurrence (*CID* 2016;65:651); consider risk/benefit for Pts needing abx w/ h/o severe or recurrent CDI (*NEJM* 2023;388:654). Avoid acid suppression/abx if possible.

Chronic Diarrhea (>4 wk)

General evaluation (*JAMA* 2016;315:2712; *Gastro* 2019;157:3)

- **Watery** (osmotic, secretory), **fatty** (malabs./maldigest.), **inflammatory**, **fxnal/structural**
- Additional hx: timing (freq, relation to meals; *nocturnal diarrhea* a/w organic causes like IBD rather than IBS), abd pain, wt loss, prior surg, chemo/XRT, diet (incl caffeine or poorly absorbed carbs/sugars), infectious sx, immunocompromised, travel, laxative use, stress
- Hx offending meds: PPI, colchicine, abx, H2RA, SSRIs, ARBs, NSAIDs, chemo, caffeine
- PEx: gen appearance (eg, BMI), signs of systemic disease, surgical scars, rectal tone/DRE
- Lab testing: CBC, metabolic profile, alb, TSH, Fe, fecal calpro; *see under each category*
- Imaging/endoscopy: colonoscopy for chronic diarrhea of unknown cause. Abd CT/MRI usually warranted if systemic problem suspected.

Osmotic (watery; ⊖ fecal fat, ↑ osmotic gap, ↓ diarrhea w/ fasting)

- Caused by ingestion of poorly absorbed cations/anions (Mg, sulfate, phos; found in laxatives) or poorly absorbed carbs (eg, mannitol, sorbitol [found in chewing gum]) or lactose if lactose intolerant. *Diarrhea resolves w/ cessation of offending substance.*
- Dx: ↑ **stool osmotic gap** (see Figure 3-2); stool pH <6 if unabsorbed carbohydrates
- **Lactose intolerance**: can be acquired after gastroenteritis, med illness, GI surg. Clin: bloating, flatulence, discomfort, diarrhea. Dx: H^+ breath test or empiric lactose-free diet. Rx: lactose-free diet & lactase tablets.

Secretory (watery; nl osmotic gap, no **Δ** diarrhea w/ fasting, nocturnal, cramps)

- Caused by secretion of anions or K+ into lumen or inhib of Na absorption → ↑ H_2O in stool
- **Infection** (bacterial toxins) most common cause (vide supra)
- **Endocrine:** Addison's, VIPoma, carcinoid, Zollinger–Ellison, mastocytosis, hyperthyroid (↑ motility). ✓ serum peptide levels (eg, gastrin, calcitonin, VIP) & urinary histamine.
- **GI neoplasm:** carcinoma, lymphoma, villous adenoma

- **Microscopic colitis:** common cause of chronic diarrhea w/ obscure origin. Often seen in middle-aged women w/ autoimmune disorders. NSAIDs, SSRIs, PPIs notable triggers. Grossly normal on colo but bx shows lymphocytic & plasmacytic infiltration of mucosa ± thickened submucosal collagen. Rx: budesonide (1st line), antidiarrheals, cholestyramine, bismuth subsalicylate; consider anti-TNFs if refractory (*Gastro* 2016;150:242).
- **Bile acid–induced diarrhea:** ileal resection or disease (eg, Crohn) → bile acids in colon → electrolyte & H_2O secretion. Rx w/ empiric bile acid binders (eg, cholestyramine).

Functional/IBS (normal osmotic gap, ↓ diarrhea with fasting): see "Dysmotility"

Malabsorption (fatty; ↑ fecal fat, ↑ osmotic gap, ↓ diarrhea w/ fasting)

- Defective mucosal absorption of nutrients b/c Δs in: mucosal surface (surgical resection) or gen. mucosal dis. (celiac, IBD). Bloating, foul-smelling, floating stools (steatorrhea).
- **Celiac disease** (*Lancet* 2022;399:2413)
  - Immune rxn in genetically predisposed Pts (~1% pop) to gliadin, a component of gluten (wheat protein) → small bowel inflammatory infiltrate → impaired absorption
  - Other s/s: Fe/folate/B_{12} defic anemia; osteoporosis; dermatitis herpetiformis; ↑ ALT/AST
  - Dx: best if eating gluten when tested; IgA tissue transglutaminase Ab (most Se), IgA anti-deaminated gliadin peptide Ab; IgA α-endomysial Ab. Duodenal bx confirms dx (blunted villi, crypt hyperplasia, inflamm infiltrate); absence of HLA-DQ2/8 excludes dx.
  - Rx: gluten-free diet; 7–30% do not respond to diet → ? wrong dx or nonadherent
  - Complic: ~5% refractory sx, risk of T-cell lymphoma and small bowel adenocarcinoma
- **Whipple disease:** infxn w/ *T. whipplei* (*Lancet* 2016;16:13)
  - Other s/s: fever, LAN, edema, arthritis, CNS Δs, gray-brown skin pigmentation, AI & MS, oculomasticatory myorhythmia (eye oscillations + mastication muscle contract)
  - Dx: bx/path, IHC, PCR. Rx: PCN + streptomycin or 3rd-gen ceph × 10–14 d → Bactrim ≥1 y.
- **Small intestinal bacterial overgrowth** (SIBO): colonic bacteria in SI → steatorrhea, B12/Fe defic, protein-losing enteropathy. A/w dysmotility (DM neuropathy, scleroderma), Δ'd anatomy (Crohn, surgery, fistulae), immune deficiency, celiac, CF. Dx w/ H^+ or ^{14}C-xylose breath testing or empiric abx. Rx w/ 7–10 d abx (rifaximin, MNZ, or FQ).
- Other: s/p short bowel resection (short bowel syndrome), chronic mesenteric ischemia, eosinophilic gastroenteritis, intestinal lymphoma, tropical sprue, *Giardia* infection

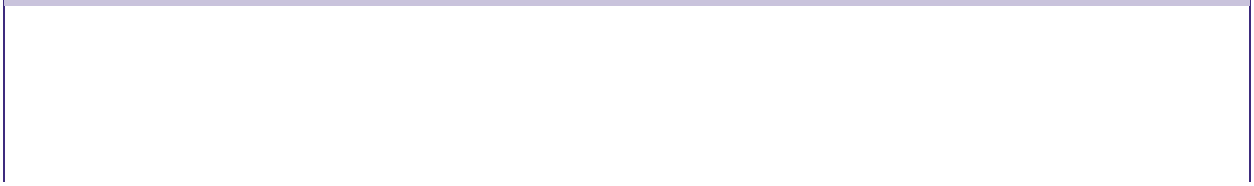
Maldigestion (fatty; ↑ fecal fat, ↑ osmotic gap, ↓ diarrhea w/ fasting)

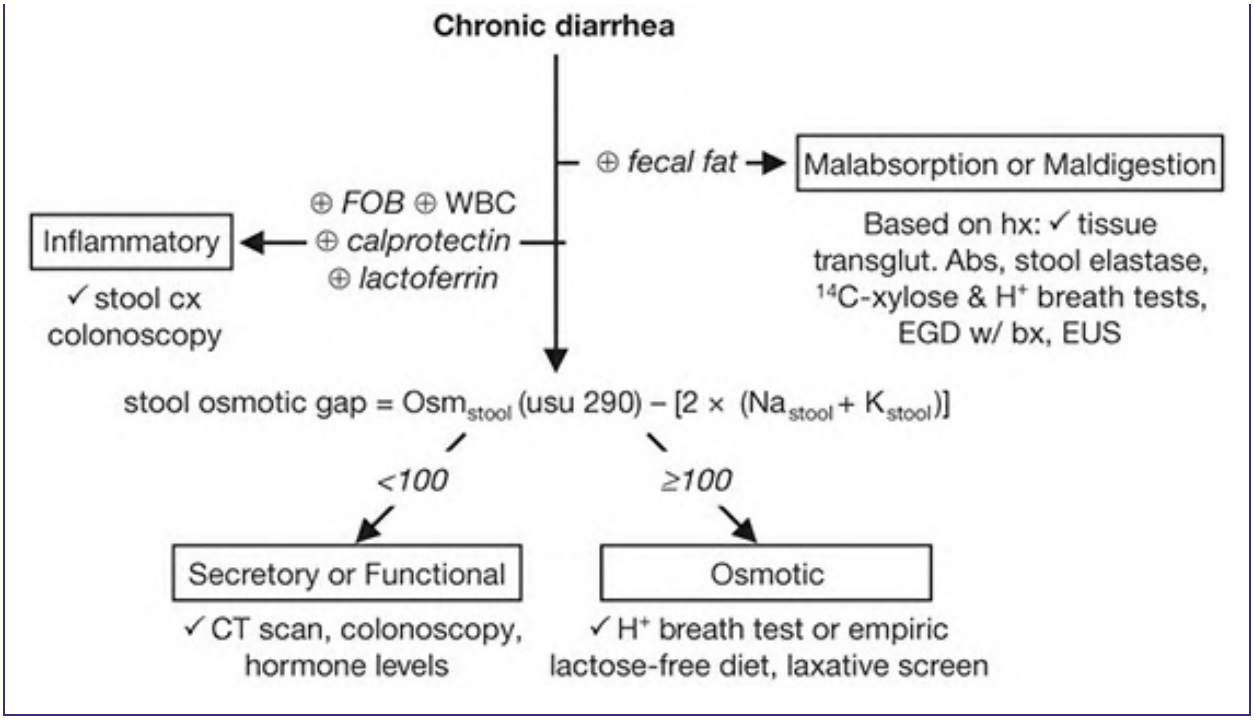
- Defective intraluminal hydrolysis of nutrients, typ. 2/2 pancreatic/hepatobiliary pathology
- **Pancreatic insufficiency:** most commonly from chronic pancreatitis or pancreatic cancer. Test w/ stool elastase, chymotrypsin levels, fecal fat, or empiric pancreatic enzyme Rx.
- ↓ **bile acids** due to ↓ synthesis (cirrhosis), cholestasis (PBC), or s/p ileal resection. Test w/ empiric bile acid replacement therapy.

Inflammatory (⊕ fecal WBC, calprotectin, lactoferrin; ⊕ FOB; fever, abd pain)

- **Infections:** chronic *C. diff*, *Entamoeba histolytica*, *Yersinia*, CMV, TB especially in immunocompromised hosts. CMV, *C. diff* notorious for causing exacerbations of IBD.
- **Inflammatory bowel disease** (Crohn, UC); fecal calprotectin helpful for ruling out IBD
- Radiation enteritis, ischemic colitis, neoplasia (colon cancer, lymphoma)

Figure 3-2 Workup of chronic diarrhea





DYSMOTILITY & NUTRITION

Functional GI disease (~30 types per Rome IV criteria; *Gastro* 2016;150:1257)

- Recurrent GI sx caused by disorders of gut–brain interaction rather than structural cause
- **Irritable bowel syndrome (IBS)** (*JAMA* 2015;313:949; *Gastro* 2022;163:118 & 137)
  Abd pain for 6+ mos a/w ≥2: improves w/ defecation, Δ stool frequency, Δ stool form
  IBS-C (constipation predominant) vs. **IBS-D** (diarrhea predominant) vs. IBS-M (mixed) vs. IBS-U (unclassified). Sx may be affected by stress, diet, lifestyle, probably microbiome.
  Treatment: cog. behavior Rx, probiotics, anti-spasmodics, exercise, neuromodulators (eg, TCA, SSRI), Δ diet (↓ fermentable carbs w/ low FODMAP diet, lactose-free diet)
  IBS-C: ↑ fiber, psyllium, laxatives, lubiprostone, linaclotide, tegaserod, tenapanor
  IBS-D: loperamide, rifaximin, eluxadoline, bile acid sequestrants, alosetron, amitriptyline
- **Cyclic vomiting syndrome (CVS):** acute recurrent vomiting; a/w marijuana use, personal or FHx of migraine. Acute Rx: antiemetics, IVF, sumatriptan (1st line, followed by aprepitant × 3 d), BDZs; prevention: TCAs/AEDs; avoid marijuana.

Gastroparesis (*Nat Rev Dis Primers* 2018;4:41)

- Delayed gastric emptying w/o mechanical obstruction, typically p/w nausea (>90%), vomiting (>80%), early satiety (60%), postprandial fullness/pain
- Etiol: DM, postsurg, post-viral, crit. illness, Parkinson, opiates, CCB, anti-cholin, idiopath
- Dx: r/o mechanical cause then gastric emptying scintigraphy; (⊕ if retained solids >4 h)
- Rx: prokinetics (metoclopramide or erythro), antiemetics for sx; feeding tube if refractory; consider pyloromyotomy, botox, G-POEM, pyloroplasty, or gastric stimulator

Paralytic ileus of the colon & small bowel (*Dis Colon Rectum* 2021;64:1046)

- Definition: loss of intestinal peristalsis in absence of mechanical obstruction
- Abd discomfort & distention, ↓ or absent bowel sounds, ± N/V, hiccups
- Typically in elderly, hospitalized, ill Pts; precipitated by: intra-abd process (surgery, pancreatitis, peritonitis, intestinal ischemia), severe illness (eg, sepsis), meds (opiates, CCB, anticholin.), metab/endo abnl (thyroid, DM, kidney failure, liver failure, hypoK), spinal cord compression/trauma, neurologic d/o (Parkinson, Alzheimer, MS)
- KUB/CT w/ colonic dilatation (in ileus, dilated loops of SB) w/o mech obstruction; cecal diam >12 cm a/w high-risk perf in Ogilvie syndrome (colonic pseudo-obstruction)
- **Treatment:** NPO, avoid offending meds, IV **neostigmine** (monitor for bradycardia), methylnaltrexone; bowel decompression w/ NGT, rectal tube, nutrition support. Ogilvie only: colonoscopic decompression; if refractory, colostomy or colectomy.

Constipation (*Annals* 2015;162:ITC1; *Nat Rev Dis Primers* 2017;3:17095; *JAMA* 2019;322:2239)

- Defined as dissatisfaction w/ defecation or (per Rome IV): ≥2 of following during last 3–6 mos ≥25% of the time: straining, lumpy/hard stools, incomplete evacuation, sensation of anorectal obstruction, manual maneuvers to facilitate defecation, stool frequency <3/wk
- **Primary etiologies:** slow transit vs. pelvic floor dyssynergia
- **Secondary etiologies** (4 Ms; *JAMA* 2016;315:185)
  Mech obstruction: malignancy, compression, rectocele, strictures
  Meds: opioids, TCAs, anticholinergics, CCB, NSAIDs, diuretics, Ca^{2+}, Fe, low-fiber diet
  Metabolic/endo: DM, hypothyroid, uremia, preg, panhypopit, porphyria, ↑ Ca, ↓ K, ↓ Mg
  Myopathy/Neuro: Parkinson, Hirschsprung, amyloid, MS, spinal injury, dysautonomia
- **Dx:** H&P w/ DRE. Labs: consider CBC, electrolytes w/ Ca, TSH. Colonoscopy if alarm sx. Anorectal manometry/balloon expulsion test; colonic transit study; defecography.
- **Treatment:** *1st line:* ↑ fluid, fiber, & exercise; emollient laxative (docusate) to soften stool
  2nd line: Bulk laxatives (psyllium, methylcellulose) to ↑ colonic residue, ↑ peristalsis. Stimulant laxatives (senna, castor oil, bisacodyl) to ↑ motility & secretion. Osmotic laxatives (Mg, $NaPO_4$ [avoid in CKD], PEG) to ↑ H_2O in colon.
  3rd line: Enema/suppository (phosphate, mineral oil, tap water, soapsuds, bisacodyl)
  After above failed: linaclotide ↑ stool freq, ↓ straining/bloating (*Am J Gastro* 2018;113:105)
  Lubiprostone (↑ secretion); methylnaltrexone and alvimopan for opioid-induced
  Plecanatide (cGMP agonist) or prucalopride (5-HT-receptor agonist) for chronic idiopathic constipation (*Gastroenterol* 2023;118:939)

Nutrition in critical illness (also see "Mechanical Ventilation") (*Crit Care* 2015;19:35)

- Enteral & parenteral with similar clinical outcomes (*Lancet* 2018;391:133)
- **Enteral** (EN): starting w/in 48 h of ICU admit may ↓ infection & mortality. Contraindic. if bowel obstruction, major GIB, uncontrolled shock. Possible complic: ischemic bowel b/c ↑ demand for splanchnic blood, aspiration PNA, metabolic abnormality.
- **Parenteral** (PN): start after 7 d if unable to tolerate EN; no clear benefit to early initiation. Contraindic: hyperosmolality, severe electrolyte disturbances, severe hyperglycemia; sepsis is *relative* contraindication. Complications: hyperglycemia, sepsis (↑ risk of fungal infections), catheter-associated thrombus, refeeding syndrome, abnl LFTs (steatosis, cholestasis, gallbladder sludge due to lack of enteric stimulation).

DISORDERS OF THE COLON

DIVERTICULOSIS

Definition & pathophysiology (*Aliment Pharm Ther* 2015;42:664)

- Acquired herniations of colonic mucosa & submucosa in areas where vasa recta penetrate
- Abnormal motility and ↑ intraluminal pressure cause protrusion of colonic wall

Epidemiology

- Risk factors: ↓ fiber, chronic constipation, obesity, smoking, physical inactivity, EtOH, NSAIDs, ↑ age (10% if <40 y; 50–66% if >80 y); ↑ red meat consumption
- **Left side** (90%, mostly sigmoid) > R side of colon (except in Asia where 75–85% R-sided)

Clinical manifestations

- Usually asx; 5–15% develop diverticular hemorrhage (see "GIB") and 10–25% diverticulitis; "SUDD": sx (abd pain ± bloating, bowel habit Δ) uncomplicated diverticular disease
- Limited data for ↑ fiber diet or avoiding nuts/seeds (*Thera Adv Gastro* 2016;9:213)

Diverticulitis

Pathophysiology (*Gastro* 2015;149:1944)

- Retention of undigested food and bacteria in diverticulum → fecalith formation → obstruction → compromise of diverticulum's blood supply, infxn, microperforation
- **Uncomplicated** (75%): microperforation → localized infection, LLQ pain, fever, ↑ WBC
- **Complicated** (25%): macroperf → abscess, peritonitis, fistula (65% w/ bladder), obstrxn

Clinical manifestations

- **LLQ abdominal pain**, **fever**, nausea, vomiting, constipation or diarrhea
- PEx ranges from LLQ tenderness ± palpable mass to peritoneal signs & septic shock
- Ddx includes IBD, infectious colitis, PID, tubal pregnancy, cystitis, colorectal cancer

Diagnostic studies

- **Abdominal CT** (I^+O^+): diverticula, bowel wall thickening, pericolic fat ± abscess, fistula
- Colonoscopy *contraindic.* acutely as ↑ risk of perforation; for Pts w/o colonoscopy in the past year, perform 6–8 wks after episode of diverticulitis to r/o neoplasm

Treatment (*JAMA* 2017;318:291; *NEJM* 2018;379:1635; *Gastro* 2021;160:906)

- Mild: outPt Rx indicated if Pt has few comorbidities and can tolerate POs
  - PO abx: (MNZ + FQ) or amox/clav for 7 d; liquid diet until clinical improvement
  - No abx is noninferior to abx in mild diverticulitis (*Clin Gastro Hepatol* 2021;19:503)
- Severe: inPt Rx if cannot take POs, narcotics needed for pain, or complications
  - NPO, IVF, NGT (if ileus); IV abx (GNR & anaerobic coverage; eg, CTX/MNZ or pip-tazo)
- Abscesses >4 cm should be drained percutaneously or surgically
- Surgery: if progression despite med Rx, undrainable abscess, free perforation
  - After source control, 4 d abx may be sufficient (*NEJM* 2015;372:1996)
  - Resection for recurrent bouts of diverticulitis on a case-by-case basis
  - Consider lower threshold for urgent & elective surgery for immunocompromised Pts

Prevention (*Gastro* 2021;160:906)

- **Maintain high-quality diet and physical activity**; avoid smoking and NSAIDs; Risk of recurrence 10–30% w/in 10 y of 1st episode; nuts, seeds ⌀ increase risk

Polyps

Pathophysiology & epidemiology (*NEJM* 2016;374:1065)

- Accumulation of mutations in colonic epithelial cell DNA affecting oncogenes & tumor suppressor genes → *tumor initiation* (formation of adenoma; *APC* loss of fxn) → *tumor progression* (adenoma → carcinoma; *K-ras* gain of fxn, *DCC, p53* loss of fxn)
- Risk factors: ↑ age, FHx (sporadic in 1° relatives, Lynch, FAP), IBD, ↑ dietary fat, central adiposity, ↑ EtOH, ↓ fiber, ↑ red meat, smoking, DM
- Protective factors: ↑ physical activity, ASA/NSAIDs, Ca^{2+} intake, HRT, ↓ BMI; possibly ↑ fiber, vitamin D, fish oil, statins, selenium
- **Neoplastic polyps**: adenomas (tubular, villous, tubulovillous dysplasia), sessile serrated adenomas/polyps (concern for interval CRC), carcinomas
- **Nonneoplastic polyps**: hyperplastic, juvenile, Peutz–Jeghers (can undergo malignant transformation), inflammatory

CRC screening (*JAMA* 2021;325:1978)

- *Colonoscopy* gold standard. Other options: FOBT/FIT yearly, flex sig q5y or flex sig q10y + FIT every year, fecal DNA testing (eg, Cologuard) q3y or CT colonography q5y; blood DNA tests emerging.
- Start screening in average risk Pts at age 45 (typically q10y unless abnl found)
- If ⊕ FHx, start age 40, or 10 y before age of dx in youngest family member, repeat q5y

INFLAMMATORY BOWEL DISEASE

Definition (*NEJM* 2020;383:2652)

- **Ulcerative colitis (UC):** inflammation of the colonic *mucosa*; *contiguous*, starting at rectum
- **Crohn disease (CD):** *transmural* inflammation anywhere along GI tract, *skip lesions*

Epidemiology & pathophysiology (*Lancet* 2016;387:156 & 2017;390:2769)

- Age of onset 15–30 y; bimodal w/ 2nd peak at 50–70 y; 1:1 M:F in N America
- Genetic predisposition (↑ Caucasian/Jewish) + environmental risk factors (smoking ↑ risk for CD, defective mucosal barrier) → T-cell dysregulation → inflammation

Ulcerative Colitis (*JAMA* 2023;330:951)

Clinical manifestations

- **Grossly bloody diarrhea**, lower abdominal cramps, tenesmus, small, frequent BM
- Extracolonic (>25%): erythema nodosum, pyoderma gangrenosum, aphthous ulcers, uveitis, episcleritis, thromboembolic events (esp. during a flare; *Lancet* 2010;375:657), AIHA, seroneg arthritis (most common), PSC (↑ risk cholangio CA, CRC)
- Several scores for severity assessment: Truelove & Witts; Mayo Score/DAI; Montreal

Diagnosis

- **Colonoscopy:** involves rectum (95%) & extends prox., circumfer., & *contig. w/in colon*
- Location: proctitis (30–60%), L-sided (15–45%), and extensive (pancolitis; 15–35%)

- Appearance: vascularity loss, friable mucosa, diffuse ulceration, *pseudopolyps* (chronicity)
- Histology: superficial chronic inflammation; crypt abscesses & architectural distortion
- Barium enema with featureless and tubular appearance of colon (*lead pipe appearance*)
- Flares: ↑ ESR & CRP (not Se or Sp); ⊕ fecal calprotectin helpful in distinguishing IBD vs. IBS and monitoring for IBD flare (*Gastro Hep* 2017;13:53); must rule out infection

Complications

- **Toxic megacolon** (5%): colon dilatation (≥6 cm on KUB), colonic atony, systemic toxicity, & ↑ risk of perf. Rx w/ IV steroids & broad-spectrum abx; surgery if needed.
- Stricture (rectosigmoid), dysmotility, anorectal dysfxn after recurrent inflammation
- ↑ Risk of CRC and dysplasia (vide infra) after 8 years of active disease
- For Pts s/p surgery w/ ileal pouch, may develop *pouchitis* (inflammation of ileal pouch, up to 1⁄2 of Pts). Rx w/ abx (MNZ, cipro), probiotics.

Prognosis

- 50% in remission at any given time. Intermittent exacerbations in 90%; continual active disease in ~18%. Prox progression in 25% at 10 y. Rate of colectomy at 10 y is 24%.
- Mortality rate of severe UC flare is <2%, & overall life expectancy in UC = non-UC Pts

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Crohn Disease (CD) (*Lancet* 2024;403:1177)

Clinical manifestations (*Nat Rev Gastro Hepatol* 2016;13:567)

- **Abdominal pain**, loose/frequent stools (up to 50% ⊕ FOBT), malaise, wt loss
- Mucus-containing, **often nonbloody diarrhea**
- N/V, bloating, obstipation if presence of obstruction; extracolonic manifestations as in UC
- Several scoring systems: CD Activity Index (CDAI), Harvey–Bradshaw Index

Diagnosis

- **Ileocolonoscopy** + **bx along w/ small bowel assessment** (eg, MR enterography)
- Small bowel/ileitis (~25%), ileocolonic (~50%), colonic (~25%); isolated upper tract rare
- Appearance: nonfriable mucosa, cobblestoning, aphthous ulcers, deep & long **fissures**
- Histology: **transmural inflammation** with mononuclear cell infiltrate, **noncaseating granulomas** (seen in <25% of mucosal bx), fibrosis, ulcers, fissures, skip areas
- Montreal classification: age at dx, disease location & behavior (stricturing vs. nonstricturing, penetrating vs. nonpenetrating), plus modifiers for upper tract & perianal disease

Complications

- **Perianal disease:** fissures, fistulas, skin tags, perirectal abscesses (in 24% of Pts; perianal disease *precedes* intestinal symptoms)
- **Stricture:** small bowel, postprandial abd pain; can lead to complete SBO & require surgery
- **Fistulas:** perianal, enteroenteric, rectovaginal, enterovesicular, enterocutaneous
- **Abscess:** fever, tender abd mass, ↑ WBC; *steroids mask sx*, ∴ need high level of suspicion
- **Malabsorption:** ileal disease/resection: ↓ bile acids abs → gallstones; ↓ fatty acid abs → Ca oxalate kidney stones; ↓ fat-soluble vitamin abs → vit D deficiency → *osteopenia*

Prognosis

- Variable at 1 y: ~50% in remission, ~20% flare, ~20% low activity, ~10% chronic active
- At 20 y, majority will have required some surgery; overall life expectancy is slightly ↓

MANAGEMENT (*Lancet* 2017;398:1756; *Mayo* 2017;92:1088)

Initial evaluation

- **H&P** (✓ for intestinal & extraintestinal manifestations) and **dx studies** as above
- **Lab:** consider CBC/diff, LFTs, iron studies, B12, folate, vit D, ESR, CRP, fecal calprotectin
- **Exclude other etiologies:** infectious (espec. TB), ischemic colitis, intestinal lymphoma, CRC, IBS, vasculitis, Behçet, celiac disease, small intestinal bacterial overgrowth
- **R/o infection** (esp. TB, HBV, CMV, O&P) before treating with immunosuppressants and biologics (although not all acutely hosp. Pts w/ IBD need infxn r/o prior to Rx)

Goals of treatment (*Ther Adv Gastro* 2015;8:143)

- Induce remission of acute flare → maintain remission; mucosal healing 1° goal
- Step-up (least → most toxic) vs. strongest → de-escalate; consider early biologic if severe

Medical Therapy for IBD (*NEJM* 2021;385:1302)	
Ulcerative Colitis (*Am J Gastrol* 2019;114:384)	
Mild	**Rectal mesalamine** or **glucocorticoids** as suppository or enema
Mild– moderate	**Oral 5-ASA:** many formulations (sulfasalazine, mesalamine, olsalazine, balsalazide) depending on disease location. Used for induction & maintenance of remission. Complications: pancreatitis, abd pain, diarrhea. **MMX budesonide:** PO budesonide released throughout colon for flare. 1st-pass metabolism ↓ systemic adverse effects of steroid.
Moderate– severe (*Gastro* 2024; 167:1314)	**PO prednisone:** 40–60 mg w/ taper over several wks to induce remission **AZA/6-MP:** 0.5–1 mg/kg; uptitrate over wks for maintenance of remission Complications: BM suppression, lymphoma, pancreatitis, hepatitis ✓ TPMT levels prior to dosing to ↓ risk of generation of toxic metabs In selected cases, add allopurinol to boost activity in non-responders **Anti-TNF:** ↑ remission rate when AZA combined w/ IFX (*Gastro* 2014;146:392); rare cases of hepatosplenic T-cell lymphoma in young men (infliximab > golimumab > adalimumab efficacy) Other agents listed below can also be considered
Severe or refractory (*NEJM* 2017; 376:1723 & 2024;391:217; *JAMA* 2019; 321:156 & 2024;332:881; *Lancet* 2023; 401:1159 & 2025;405:33)	**IV steroids:** 100 mg hydrocort q8h or 16–20 mg methylpred q8h to induce remission w/ plan to taper & switch to non-steroid maintenance **Cyclosporine:** for severe flares refractory to steroids, 2–4 mg/kg infusion × 7 d w/ goal to Δ to maintenance medication (eg, AZA/6-MP) **Anti-TNF** (infliximab, adalimumab, & golimumab): for steroid-refractory flares or to maintain remission. Complic: reactivation of TB (✓ PPD prior to Rx) or viral hepatitis; small ↑ risk NHL; lupus-like rxn, psoriasis, MS, CHF. **Other:** vedolizumab (α4β7 integrin inhib.); tofacitinib, upadacitinib (JAK inhib.); ustekinumab, risankizumab, guselkumab, mirikizumab (IL-12/23 inhib.); ozanimod or etrasimod (sphingosine-1-phosphate receptor modulator) *Investigational:* fecal microbiota transplant
Crohn's Disease (*JAMA* 2021;325:69; *Gastro* 2025;168:33)	

Mild	**Oral 5-ASA:** for colonic CD **Symptom control:** loperamide/cholestyramine for diarrhea management
Mild–mod	**PO budesonide:** enteric-coated for ileal release (taper over 3 mos)
Moderate– severe (*Gastro* 2021; 160:2498; 2025;168:33)	**PO prednisone:** same as UC, for inducing remission, not maintenance **AZA/6-MP:** same as UC; ↑ remission w/ AZA+IFX (*NEJM* 2010;362:1383) **MTX:** 15–25 mg IM/SC or PO qwk for maintenance; 1–2 mo to take effect **Biologics:** anti-TNF (inflixi, adalimumab > certolizumab); consider combo w/ AZA/6-MP or vedolizumab, ustekinumab, risankizumab, upadacitinib
Severe or refractory (*Gastro* 2021; 160:2501)	**IV steroids:** same as UC, for inducing remission, not maintenance **Anti-TNF:** same as above, 1st line w/ perianal fistula **Anti-integrin** (vedolizumab); **anti-IL-23 ± 12** (vide supra; *Lancet* 2024;404:2423) **JAK inhib.** (tofacitinib, upadacitinib) if TNF failure

Surgery

- **UC:** colectomy if sx refractory to or intolerable side effects from meds, CRC, perforation, toxic megacolon, uncontrolled hemorrhage. Often *ileal pouch-anal anastomosis* (IPAA).
- **CD:** resection if refractory; surgery for strictures; diverting ileostomy for perineal disease

Cancer screening (*NEJM* 2015;372:1441)

- **Colon cancer:** risk in UC ~2% at 10 y, ~8% at 20 y, ~18% at 30 y. Similar for pancolonic CD, plus risk of small bowel cancer as well. Dysplasia best marker for risk. Other risk factors include: PSC, ⊕ FHx, greater extent of disease, stricture, & pseudopolyps.
- **Surveillance:** *colo* w/ random bx 8 y after dx to eval for dysplasia, q1–3y thereafter based on risk factors. *Chromoendoscopy* using dye to stain high-risk lesions for targeted bx may be preferable. If high-grade dysplasia or dysplasia-assoc. lesion/mass → colectomy.

INTESTINAL ISCHEMIA

Acute Mesenteric Ischemia

Definition and causes (*NEJM* 2016;374:959)

- Reduced or absent blood flow to small intestine, typically caused by *arterial* (ie, SMA or its branches) occlusion or transient hypoperfusion or less often by *venous* occlusion
- **Arterial embolism** (~40–50%): embolic occlusion to SMA (has narrow take-off angle), often in setting of AF, valvular disease incl. endocarditis, athero plaque in aorta
- **SMA thrombosis** (~20–30%): typically due to athero at origin of SMA; other risk factors incl. vascular injury from abd trauma, infxn, or mesenteric dissections/aneurysms
- **Nonocclusive mesenteric ischemia** (~10%): transient intestinal hypoperfusion due to ↓ CO, athero, sepsis, drugs that ↓ gut perfusion (pressors, cocaine, amphetamines)
- **Mesenteric venous thrombosis** (MVT, ~5%): a/w hypercoag. states, portal hypertension, IBD, malignancy, inflammation (pancreatitis, peritonitis), pregnancy, trauma, surgery
- **Focal segmental ischemia of small bowel** (<5%): vascular occlusion to small segments of small bowel (vasculitis, atheromatous emboli, strangulated hernias, XRT)

Clinical manifestations

- Arterial occlusion: **sudden intense abd pain out of proportion to tenderness on exam**
- Venous occlusion: *often more insidious in onset*, intermittent pain with peaks and valleys
- Nonocclusive: abd distention & pain, n/v, **lower GI bleeding** due to mucosal sloughing; often occurring after episode of hypoperfusion (eg, cardiac event or shock)
- Exam ranges: unremarkable ± abd distention to peritoneal (infarction); ⊕ **FOBT ~75%**

Diagnostic studies

- Dx relies on high level of suspicion; rapid dx essential to avoid infarction (occurs w/in hrs)
- Mortality 20 to >70% if bowel infarcted; dx prior to infarction strongest predictor of survival
- Laboratory: often nl; ~75% ↑ WBC; ↑ amylase, LDH, PO_4, D-dimer; ~50% ↑ lactate (late)
- KUB: nl early before infarct; "thumbprinting," ileus, pneumatosis in later stages
- **CT angiography** (arterial phase): noninvasive test of choice; *venous* phase for dx MVT
- **Angiography:** gold standard; potentially therapeutic; indicated if vasc occlusion suspected

Treatment (*NEJM* 2016;374:959; *World J Emerg Surg* 2017;12:38)

- IVF, NPO, **optimize hemodynamics** (minimize pressors), **broad-spectrum abx**, **anticoagulation** w/ heparin ± **tPA** (for occlusive disease), **IV papaverine** (vasodilator; for non-occlusive mesenteric ischemia)
- If evidence of peritonitis: to OR for surgical endovascular therapies & bowel resection
- **SMA thrombosis:** percutaneous (stenting) or surgical revascularization
- **SMA embolism:** embolectomy (catheter-based aspiration vs. surgical)
- **Nonocclusive:** correct underlying cause (esp. cardiac)
- **Mesenteric venous thrombosis:** 3–6 mo anticoag after initial heparinization. Fibrinolysis or thrombectomy typically reserved for hemodynamic instability or refractory sx.
- **Focal segmental ischemia:** typically surgical resection

Chronic Mesenteric Ischemia

- Pathophysiology: ↓ blood flow to gut typically because of mesenteric atherosclerosis
- Sx: "intestinal angina" = **postprandial abd pain**, early satiety, & ↓ wt due to fear of eating. If pain becomes constant → could represent acute thrombosis (vide supra).
- Dx: duplex U/S or CTA; angiography gold stnd; gastric tonometry exercise testing
- Treatment: surgical revascularization (1st line); angioplasty ± stenting; TPN for nutrition

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Ischemic Colitis

Definition & pathophysiology

- Nonocclusive disease 2° to Δs in systemic circulation or anatomic/fxnal Δs in local mesenteric vasculature; often underlying etiology unknown, frequently seen in elderly
- "Watershed" areas (splenic flexure & rectosigmoid) most susceptible; 25% involve R side

Clinical manifestations, diagnosis, & treatment

- Usually p/w **cramping LLQ pain w/ overtly bloody stool;** fever and peritoneal signs should raise clinical suspicion for infarction
- Disease spectrum: reversible colopathy (35%), transient colitis (15%), chronic ulcerating colitis (20%), resulting stricture (10%), gangrene (15%), fulminant colitis (<5%)
- Dx: **flex sig/colonoscopy** or **CT abd/pelvis** to make diagnosis; r/o IBD, infectious colitis
- Treatment: bowel rest, IV fluids, broad-spectrum abx, serial abd exams; **surgery** for infarction, fulminant colitis, hemorrhage, failure of med Rx, recurrent sepsis, stricture

- Resolution w/in 48 h w/ conservative measures occurs in >50% of cases

PANCREATITIS

Acute Pancreatitis (*Lancet* 2020;396:726; *JAMA* 2021;325:382)

Pathogenesis

- Pancreatic duct and acinar injury via direct or indirect toxicity → impaired secretion and premature activation of digestive enzymes → autodigestion and acute inflammation

Etiologies (*JAMA* 2021;325:382)

- **Gallstones** (40%): ♀ > ♂; usually due to small stones (<5 mm) or microlithiasis/sludge
- **Alcohol** (30%): ♂ > ♀; 4–5 drinks/day over ≥5 yrs; usually chronic w/ acute flares
- Metabolic: hypertrig. (2–5%; TG >1000; type I & V familial hyperlipidemia); hyperCa
- Drugs (<5%): 5-ASA, 6-MP/AZA, ACEI, cytosine, ddI, dapsone, estrogen, furosemide, GLP-1RA, glucocorticoids, INH, MNZ, pentamidine, statins, sulfa, thiazides, tetracycline, valproate
- Anatomic: divisum, annular pancreas, duodenal duplication cysts, sphincter of Oddi dysfxn
- Autoimmune (vide infra)
- Familial: suspect if age <20 y; (often a/w mutation in PRSS1, SPINK1, or CFTR gene)
- Infections: ascaris, *Clonorchis*, coxsackie, CMV, EBV, HIV, mumps, mycoplasma, TB, toxo
- Ischemia: shock, vasculitis, cholesterol emboli
- Neoplastic: panc/ampullary tumors, mets (RCC most common, breast, lung, melanoma)
- Post-ERCP (5%): Ppx w/ PR indomethacin can ↓ sx; temporary panc duct stent if high risk
- Trauma: blunt abdominal trauma, post-pancreatic/biliary surgery

Clinical manifestations

- **Epigastric abdominal or LUQ pain (90%)**, 1⁄2 w/ bandlike pain radiating to back
- 10% pain-free (due to analgesic/steroid use, immunosuppressed, ΔMS, ICU); ∴ ✓ lipase in unexplained shock, periumbilical or flank (Cullen or Grey Turner signs) bruising
- **N/V (90%),** abd tenderness/guarding, ↓ bowel sounds, jaundice if biliary obstruction
- Ddx: acute cholecystitis, perforated viscus, SBO, mesenteric ischemia, IMI, AAA leak, distal aortic dissection, ruptured ectopic pregnancy
- **Early phase** (<1 wk): possible SIRS ± organ failure; **late** (>1 wk): local complications (qv)

Diagnostic studies (*Gastro* 2024;167:673)

- **Dx requires 2 of 3:** characteristic abd pain; lipase or amylase >3× ULN; ⊕ imaging
- Laboratory: levels of amylase & lipase do *not* correlate w/ severity of disease
  - ↑ **amylase**: rises w/in hrs, normalizes w/in 3–5 d (sooner than lipase) false ⊖: 20% EtOH pancreatitis; 50% hypertriglyceridemia (assay interference) false ⊕: other abd or salivary gland process, acidemia, ↓ GFR, macroamylasemia
  - ↑ **lipase**: longer $t_{1/2}$ than amylase >3× ULN 99% sensitive, 99% specific for acute pancreatitis >10k has 80% PPV for biliary dx, 99% NPV for EtOH (*Dig Dis Sci* 2011;56:3376) false ⊕: renal failure, other abd process, DKA, HIV, macrolipasemia
  - ALT >3× ULN has 95% PPV for gallstone pancreatitis (*Am J Gastro* 1994;89:1863)
- Imaging studies (*Am J Gastro* 2013;108:1400)
  - **Abd U/S:** bowel gas often obscures pancreas visualization; however, *should be ordered to r/o biliary etiology* (ie, gallstones, BD dilatation)
  - **Abd CT:** not rec with contrast for first 3 days (local complic. not yet visible & concern for AKI

w/ IV contrast). However, if persistent pain and/or clinical deterioration after 48–72 h, CT(I^+) useful to r/o local complications (necrosis, fluid collections).

MRI/MRCP: Can detect necrosis, assess for stones & ductal disruption earlier than CT

Endoscopic U/S (EUS): useful for occult biliary disease (microlithiasis)

Severity (*Gastro* 2018;154:1096)

- Severity defined by presence of organ failure (AKI, resp failure, GIB, shock) & local or systemic complic. (panc necrosis, fluid collections, gastric outlet obstrxn, splenic & PVT)
  - **Mild:** 80% of cases; no organ failure or local/systemic complic.; low mortality
  - **Moderate:** transient (<48 h) organ failure ± local/systemic complic., high morbidity
  - **Severe:** persistent (≥48 h) organ failure, very high mortality

Prognosis (*NEJM* 2016;375:1972)

- **Ranson's, APACHE II:** predict severity at 48 h using multiple physiolog. criteria; poor PPV
- **BISAP:** simple 5-point scoring system (BUN >25, impaired MS, SIRS, age >60 y, pleural effusion) used w/in first 24 h; score ≥3 predicts ↑ risk of organ failure, mortality
- **CTSI:** CT data at 48–72 h (fluid collect., necrosis) to predict mortality; lags behind clinical sx

Treatment (*JAMA* 2020;323:2331; *NEJM* 2022;387:989; *Am J Gastro* 2024;119:419)

- **Fluid resusc. (moderate):** 10 mL/kg IVB for hypovolemia → 1.5 mL/kg/hr (more aggressive does not improve outcomes & can cause fluid overload). Goal ↓ BUN & Hct over 12–24 h. ✓ UOP (goal 0.5–1 mL/kg/hr); LR superior to NS (↓ SIRS; avoid if ↑ Ca).
- **Nutrition** (*NEJM* 2014;317:1983; *Gastro* 2018;154:1099)
  - Early (w/in 24 hrs) oral feeding as tolerated
  - Mild: start feeding once without N/V or ileus; may not need to be completely pain free or have nl lipase. Low-fat low-residue diet as safe as liquid diet and a/w shorter LOS.
  - Severe: early (w/in 48–72 h) enteral nutrition indicated and preferred over TPN b/c ↓ infectious complications. Nasogastric noninferior to nasojejunal feeding.
- **Analgesia:** IV opioids (monitor respiratory status, adjust dosing if ↑ renal impairment)
- **Gallstone pancreatitis:** urgent (w/in 24 h) ERCP w/ sphincterotomy if cholangitis, sepsis, or Tbili ≥5. If mild, CCY during initial hosp. to ↓ risk of recurrence (*Lancet* 2015;386:1261); defer surgery if necrotizing panc. until improvement in inflam. & fluid collections.
- **Hypertriglyceridemia:** insulin gtt (activates lipoprotein lipase), fibrates, ± apheresis
- No role for Ppx abx in absence of infectious complications (*Am J Gastro* 2024;119:419)

Complications

- Systemic: ARDS, abdominal compartment syndrome, AKI, GIB (pseudoaneurysm), DIC
- Metabolic: hypocalcemia, hyperglycemia, hypertriglyceridemia
- Fluid collections:
  - **Acute fluid collection:** seen early; not encapsulated; asx; often resolve in 1–2 wk
  - **Pseudocyst:** ~4 wk after initial attack, encapsulated. No need for Rx if asx (regardless of size/location). If sx → endoscopic (*Gastro* 2013;145:583) vs. perc/surg drainage.
- Pancreatic necrosis: nonviable pancreatic tissue.
  - **Sterile necrosis:** if asx, can be managed expectantly, no role for Ppx abx
  - **Infected necrosis**: most often GN gut organism; high mort. Rx w/ carbapenem, pip/tazo, or [(3^{rd} gen ceph or FQ) + MNZ]. CT-guided FNA if deterioration despite abx. If stable, defer drainage >4 wk to allow liquefication & WOPN (qv). If sx or unstable, perc. drainage & minimally invasive surgical debridement or endoscopic necrosectomy.
  - **WOPN** (walled off panc. nec.): fibrous wall surrounds necrosis over ≥4 wk; endoscopic or perc. drainage (preferred over open necrosectomy) if infected or symptomatic
- Peripancreatic vascular complications: pseudoaneurysm, abdominal compartment syndrome, splanchnic venous thrombosis (splenic vein most common site)

Chronic Pancreatitis (*Lancet* 2025;404:2605)

Pathogenesis & etiology (*JAMA* 2019;322:2422; *Am J Gastro* 2020;115:333)

- Often recurrent acute attacks → inflam infiltrate → fibrosis → loss of exocrine & endocrine tissue. Pancreatic insuffic. (DM, fat/protein malabsorption) when 90% panc fxn lost.
- TIGAR-O: **T**oxic-metabolic (60–80% due to EtOH; smoking), **I**diopathic, **G**enetic (PRSS1, SPINK1, CFTR, CTRC, CASR), **A**utoimmune, **R**ecurrent panc., **O**bstruction

Clinical manifestations

- Epigastric pain, N/V; over time can be painless; signs of exocrine insuff (steatorrhea, wt loss) or endocrine insuff (DM: polydipsia, polyuria); 13× ↑ risk of pancreatic cancer

Diagnostic studies (*Pancreas* 2014;43:1143; *Am J Gastro* 2020;115:322)

- Labs: amylase/lipase ↑ early, may be nl later. ⊕ fecal fat, ↓ stool elastase & A1AT if panc insuff. Mixed TG breath test alternative to stool elastase. ✓A1c, consider IgG4/ANA & genetics if young or ⊕ FHx. If dx w/ CP, measure baseline fat-soluble vit. (ADEK).
- Imaging: CT/MRI 1st line (calcifications often seen). ERCP/MRCP/EUS: high Se for dx; may show stricture, dilated ducts. IV secretin stim w/ MRI may ↑ dx yield.

Treatment (*JAMA* 2019;322:2422; *Lancet* 2020;396:499; *Am J Gastro* 2020;115:333)

- Pancreatic enzyme replacement (may ↓ pain by reducing CCK). Rx routine vitamin D & Ca.
- Pain control: smoking & EtOH cessation; analgesics (start w/ non-opioids; eg, pregabalin); endoscopy (stone removal or stenting strictures), surgery for obstructive CP if endoscopic Rx unsuccessful; celiac nerve plexus block

Autoimmune Pancreatitis

Pathogenesis (*Am J Gastro* 2018;113:1301; *CGH* 2019;17:1937)

- Type 1: lymphoplasmacytic sclerosing w/ dense fibrosis; ↑ IgG4; relapse in up to 60%
- Type 2: idiopathic duct-centric pancreatitis; minimal ↑ IgG4; a/w IBD (UC); relapse <10%

Clinical manifestations

- Type 1 p/w obstructive jaundice, may have little or no abd pain. Type 2 p/w acute panc.
- Can be primary or in a/w IgG4 cholangiopathy, salivary gland disease (eg, Sjögren's), mediastinal or RP fibrosis, interstitial nephritis, autoimmune thyroiditis, UC/PSC, RA

Diagnosis

- Labs: cholestatic LFTs (↑ Aϕ > AST/ALT), ↑ γ-globulins and IgG4, ⊕ ANA, RF
- HISORt criteria: Histology, Imaging ("sausage pancreas," bile duct stricture), Serology, other Organ involvement, Response to therapy

Treatment

- Glucocorticoids 1st line; immunomod. (AZA, MMF, cyclophosphamide, rituximab) if relapse

ABNORMAL LIVER TESTS

Tests of hepatocellular injury or cholestasis (*J Clin Transl Hepatol* 2017;5:394)

- **Aminotransferases** (AST, ALT): intracellular enzymes released 2° necrosis/inflammation
  ALT more specific for liver than is AST (heart, skeletal muscle, kidney, brain, RBC/WBC)
  ↑ levels seen w/ most types of hepatocellular injury; AST > ALT → MSK injury, MI
- **Alkaline phosphatase** (Aϕ): enzyme bound in hepatic canalicular membrane ↑ levels seen w/ biliary obstrxn, intrahepatic cholestasis or infiltration of the liver also found in bone, intestines, kidney, placenta if isolated elevation, confirm from liver w/: ↑ GGT (or ↑ 5′-NT or fractionation)
- **Bilirubin:** product of heme metab (unconjugated, "indirect") carried by alb to liver where taken up for conjugation ("direct") to make soluble, then excreted into bile
  Indirect hyperbili: hemolysis, enzymatic disorders (eg, Crigler–Najjar, Gilbert's)
  Direct hyperbili: cholestasis, enzymatic disorders (eg, Dubin–Johnson, Rotor's, et al.)
  Jaundice when bili >2.5 mg/dL (esp. in sclera or under tongue); direct ↑ urine bili

Tests of hepatic function

- **Albumin:** marker for liver protein synthesis, can help differentiate acute vs. chronic liver failure, may be normal in acute hepatocellular injury ($t_{1/2}$ ~15–18 d)
- **Prothrombin time** (PT): depends on synthesis of coag factors by liver (except FVIII); b/c $t_{1/2}$ of some factors (eg, V, VII) is short, ↑ PT can occur w/in hrs of liver dysfxn

Patterns of LFTs				
Pattern	**ALT**	**AST**	**Aϕ**	**Bilirubin**
Hepatocellular	↑↑	↑↑	±↑	±↑ (direct)
Viral hepatitis, MASLD	Often ALT > AST		±↑	±↑ (direct)
Alcohol-assoc hepatitis	AST:ALT ≥ 2:1		±↑	±↑ (direct)
Ischemic hepatitis	↑↑↑	↑↑↑	↑↑	↑↑ (direct)
Wilson disease	↑	↑	Aϕ:Tbili <4 (if fulminant)	
Cholestatic	±↑	±↑	↑↑	↑↑ (direct)
Infiltrative	near nl	near nl	↑↑	±↑
Nonhepatic				
Skeletal muscle injury	AST >> ALT (early)		nl	nl
Bone disease	nl	nl	↑ (w/ nl GGT)	nl
Hemolysis	nl	nl	nl	↑ (indirect)

- **R-value** = ratio of ALT:Aϕ normalized to ULN for each = (ALT/ULN) ÷ (Aϕ/ULN)
  R >5 suggests hepatocellular injury, <2 suggests cholestatic injury, 2–5 suggests mixed

Acute mild-to-moderate elevation in ALT/AST (<15× ULN)

- Assess risk of **EtOH/drug/toxin**: H&P; in EtOH AST:ALT ratio >2:1
- Obtain abdominal imaging to r/o cirrhosis, congestion, or biliary obstruction (mixed LFTs)
- Other infectious etiologies: tick-borne illnesses, CMV/EBV, COVID-19, others

- Can be initial manifestation of chronic etiologies noted below

Chronic mild-to-moderate elevation in ALT/AST (<15× ULN)

- **Viral hepatitis**: ✓ HBsAg, anti-HBs, anti-HBc, anti-HCV/HCV RNA, IgM anti-HAV
- **MASLD**: consider BMI, ✓ lipid panel, Hb_{A1c}, liver U/S
- Other etiologies of cirrhosis (qv)
  Hemochromatosis: ✓ TIBC, serum iron, serum ferritin
  Wilson disease: serum ceruloplasmin, urine Cu
  α-1 antitrypsin (can cause liver disease w/o lung involvement)
- Chronic autoimmune hepatitis ✓ ANA, ASMA, anti-LKMA, IgG, SPEP
- TSH (both hypo & hyperthyroidism associated with abnormal LFTs), celiac disease
- If workup negative, consider liver bx

Acute severe elevation in ALT/AST (>1000)

- Massive elevations (>5000) usually due to ischemic hepatitis or drug-induced hepatitis
- **Ischemia**: hypotension, shock or severe HF (often >50× ULN), Budd–Chiari; usually diagnosed based on clinical hx + U/S w/ Doppler; ratio ALT:LDH <1.5 if ischemic because of concomitant ↑ LDH (vs. ratio >1.5 w/ toxins, viruses)
- **Meds/toxins (DILI)**: acetaminophen, meds (eg, INH, amio, nitrofurantoin, ICI), OTC/herbal, cocaine (nb, EtOH should not produce this degree of elevation). ✓ livertox.nih.gov website. Obtain acet. level, tox screen.
- **Acute viral infection**: hepatitis A–E or reactivation of HBV, EBV/CMV
- Acute autoimmune hepatitis (qv): ✓ IgG, ANA, ASMA
- Acute biliary obstruction (often with rise & rapid fall in ALT/AST, Aϕ takes longer to rise & fall): start w/ liver U/S, if unrevealing obtain CT or MRCP
- Rhabdomyolysis and heat stroke

Figure 3-3 Approach to abnormal liver tests with cholestatic pattern

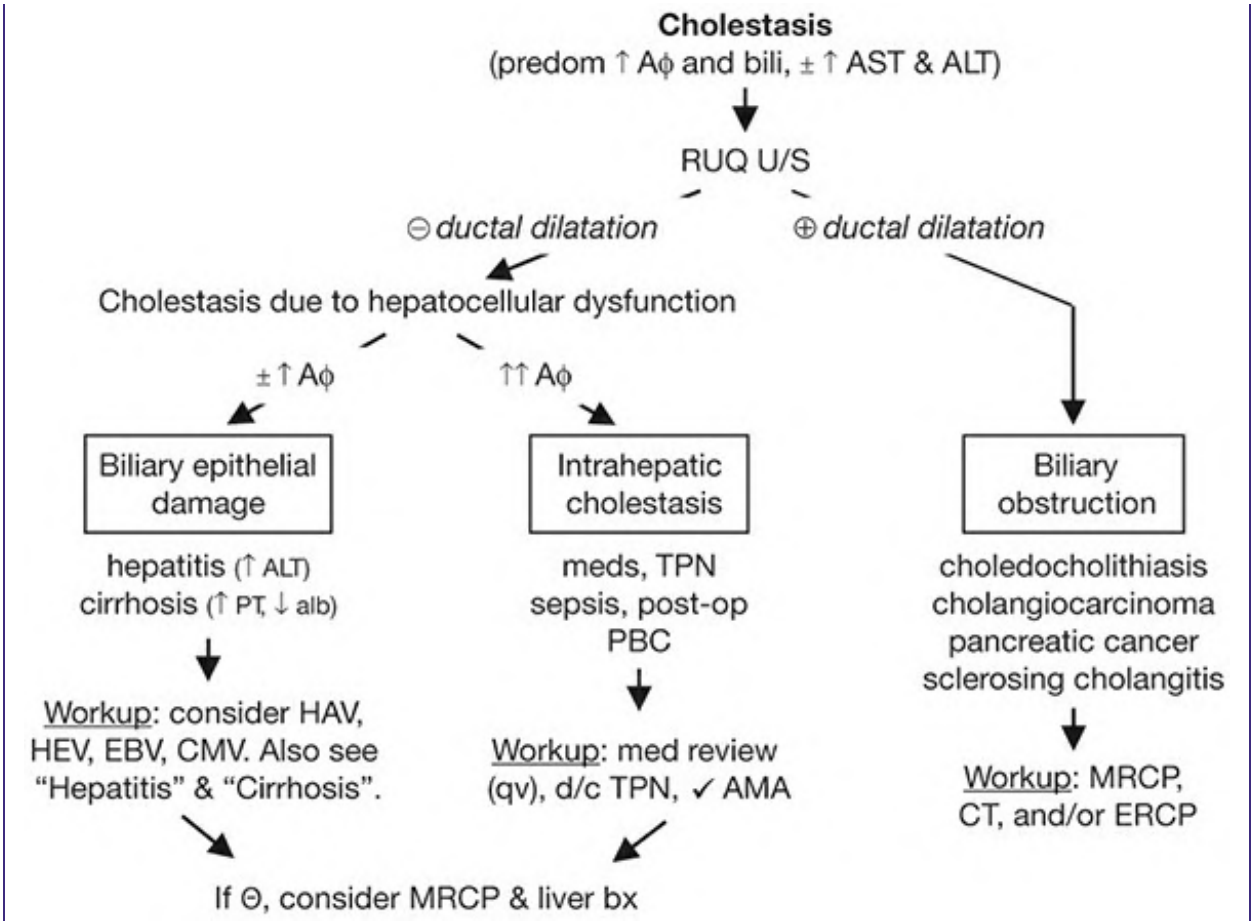
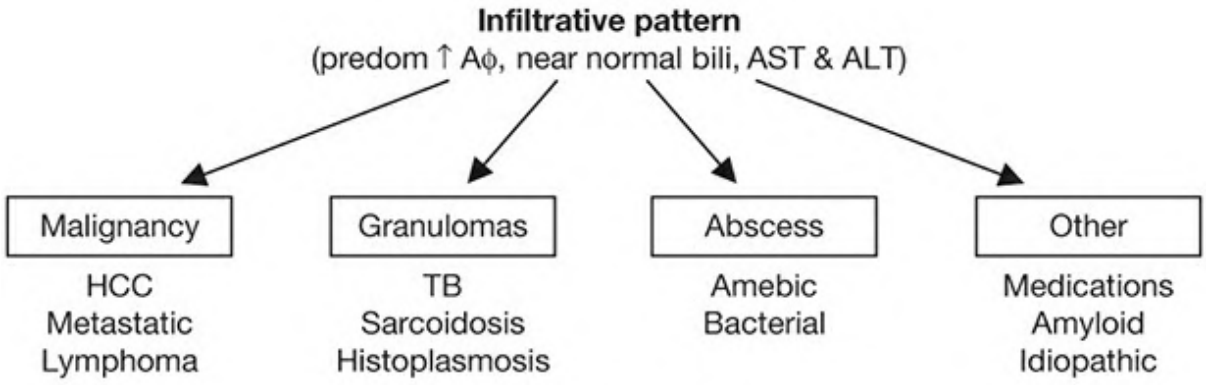


Figure 3-4 Approach to abnormal liver tests with infiltrative pattern



Medication Causes of Abnormal LFTs (http://livertox.nih.gov; *NEJM* 2019;381:264)		
Hepatocellular	**Cholestatic**	**Mixed**

acarbose acetaminophen allopurinol amiodarone azathioprine clindamycin fibrates hydralazine ICIs Isoniazid ketoconazole methotrexate mirtazapine nitrofurantoin (some) NSAIDs phenytoin	prednisone protease inhibitors pyrazinamide risperidone statins sulfonamides tamoxifen tetracyclines TNF-α inhibitors trazodone tricyclics valproic acid	ACE inhibitors anabolic *steroids* azathioprine cephalosporins chlorpromazine estrogens macrolides methimazole	6-MP OCP penicillins protease inhibitors sulfonamide terbinafine tricyclics	amox-clav azathioprine carbamazepine clindamycin mirtazapine nitrofurantoin penicillins phenobarbital phenytoin protease inhibitors sulfonamides trazodone tricyclics valproic acid verapamil

HEPATITIS

VIRAL

Hepatitis A (ssRNA; 5% of acute viral hepatitis in U.S.; *MMWR* 2018;67:1208; *CDC* 2022)

- Transmission & RFs: fecal–oral route; contam. food, water, shellfish; daycare ctr; intl travel
- Incubation: 2–6 wk; no chronic carrier state; once antibody forms → lifelong immunity
- Sx: ↓ appetite, malaise, fever, N/V, RUQ pain, jaundice; rarely ALF (↑ w/ chronic HCV)
- Diagnosis: acute hepatitis = ⊕ IgM anti-HAV; past exposure = ⊕ IgG anti-HAV (⊖IgM)
- Rx for acute HAV: supportive care; refer to liver txplnt center if acute liver failure
- Vaccinate if: MSM, IVDU, chronic liver disease, international travel; Havrix (2 doses)

Hepatitis B (dsDNA; ~16% of acute viral hepatitis in U.S.; *NEJM* 2023;388:55; *CDC* 2022)

- Transmission: blood (IVDU, transfusion), sexual, perinatal (vertical)
- Incubation: 6 wk–6 mo (mean 12–14 wk)
- Acute infxn: 70% subclinical, 30% jaundice, <1% acute liver failure (up to 60% mortality)
- Chronic infxn: HBsAg ⊕ >6 mo in <5% of adult-acquired (↑ if immunosupp), >90% of perinatal; ~40% chronic HBV → cirrhosis (↑ risk w/ HCV, HDV, or HIV coinfxn, EtOH)
- HCC: ↑ risk if cirrhosis, ⊕ FHx HCC, African >20 y old, Asian ♂ >40 y old or ♀ >50 y old, or >40 y old w/ ↑ ALT ± HBV DNA >2000. Screen w/ AFP & U/S q6mo.
- Extrahepatic syndromes: PAN (<1%), membranous nephropathy, MPGN, arthritis
- Serologic and virologic tests (screening guidelines: *Hepatology* 2018;67:1560)
  - HBsAg: appears before sx; used to screen blood donors; persists >6 mo = chronic HBV
  - HBeAg: evidence of viral replication and ↑ infectivity
  - IgM anti-HBc: 1st Ab to appear; indicates acute infection window period = HBsAg becomes ⊖, anti-HBs not yet ⊕, anti-HBc only clue to infxn
  - IgG anti-HBc: indicates previous (HBsAg ⊖) or ongoing (HBsAg ⊕) HBV infection
  - anti-HBe: indicates waning viral replication, ↓ infectivity
  - anti-HBs: indicates resolution of acute disease & immunity (sole marker after vaccination)
  - HBV DNA: presence in serum correlates w/ active viral replication in liver

Diagnosis	HBsAg	anti-HBs	anti-HBc	HBeAg	anti-HBe	HBV DNA
Acute hepatitis	⊕	⊖	IgM	⊕	⊖	⊕
Window period	⊖	⊖	IgM	±	±	⊕
Resolved	⊖	⊕	IgG	⊖	±	⊖
Immunization	⊖	⊕	⊖	⊖	⊖	⊖
Chronic hepatitis *HBeAg* ⊕	⊕	⊖	IgG	⊕	⊖	⊕
Chronic hepatitis *HBeAg* ⊖	⊕	⊖	IgG	⊖	⊕	±*

*Precore mutant: HBeAg not made, but anti-HBe can develop due to x-reactivity w/ HBcAg; a/w ↑ HBV DNA

- **Treatment for acute HBV:** supportive; hospitalize for Δ MS or ↑ INR (liver transplant center); consider antiviral therapy if severe or protracted course

Phases of Chronic HBV Infection						
Phase	**ALT (ULN*)**	**sAg**	**DNA (IU/mL)**	**eAg**	**Liver histology (inflam/fibrosis)**	**Rate of cirrhosis**
HBeAg ⊕ HBV infxn (Immune tolerant)	Nl	High	≥10^6	⊕	Minimal	<0.5%/y
HBeAg ⊕ hepatitis (Immune active)	≥2×	High	≥20k	⊕	Moderate to severe	2–5.5%/y
HBeAg ⊖ HBV infxn (Inactive carrier)	Nl	Low	≤2k	⊖	Min necroinflam; variable fibrosis	0.05%/y
HBeAg ⊖ hepatitis (Chronic hep B)	≥2×	Inter	≥2k	⊖	Moderate to severe	8–10%/y
Resolved	Nl	⊖	⊖	⊖	No inflam	Variable

*ALT ULN <35 U/L for ♂, <25 U/L for ♀. (Adapted from *Hepatology* 2018;67:1560)

- **Rx chronic HBV w/ antivirals if:** (1) immune active phase; (2) HBeAg ⊖ chronic HBV; (3) cirrhosis w/ HBV DNA ≥2K; (4) decomp. cirrhosis due to HBV; (5) acute liver failure due to acute HBV; (6) special pop: preg (3rd trimester w/ HBV DNA ≥200k), inactive carriers treated w/ immunosuppression, HCC, HCV coinfxn
- **Entecavir** or **tenofovir disoproxil fumarate (TDF) or alafenamide (TAF):** nucleo(s/t)ide analogs, well tolerated, low resist.; at 5 y, HBeAg seroconversion is 30–40% & loss of HBsAg is 5–10%. Tenofovir preferred if h/o lamivudine resist.; no known tenofovir resist. to date. Small risk of bone loss & kidney dysfxn w/ TDF vs. TAF.
- Rx duration: (1) HBeAg ⊕ immune active w/o cirrhosis: if seroconversion (HBeAg ⊖, anti- HBe ⊕), can stop after 1 y if ALT nl & HBV DNA suppressed or until HBsAg clears; (2) HBeAg ⊖ immune reactivation: indefinite; (3) cirrhosis: indefinite
- If undergo liver transplant: HBIG + nucleo(s/t)ide analogue effective in preventing reinfection
- HIV/HBV *coinfection:* Rx w/ 2 drugs active against both HBV & HIV (https://hivinfo.nih.gov)
- Immunosuppression: prior to initiating chemoRx, anti-TNF, rituximab, steroids (>20 mg/d >1 mo), screen for HBV; Rx if mod-to-high risk of reactive (incl anti-HBs ⊕ getting ritux.)
- Postexposure (risk infxn ~30%) Ppx: HBIG → vaccine (if unvac or known nonresponder)

Hepatitis C (ssRNA; ~79% of acute viral hepatitis in U.S.; *Lancet* 2023;402:1085; CDC 2022)

- Transmission: blood (IVDU, transfusion before 1992) > sexual; 20–30% w/o clear precipitant
- Incubation: 1–5 mo; mean 6–7 wk
- Acute infxn: 80% subclinical; 10–20% sx hepatitis w/ jaundice; acute liver failure rare; spont clearance a/w *IL28B* & HLA class II genotypes (*Annals* 2013;158:235)
- Chronic: up to 85% → chronic hepatitis, 20–30% of whom develop cirrhosis (after ~20 y) ↑ risk of cirrhosis in men, EtOH, HIV, smokers; HCC in 1–4% of Pts w/ cirrhosis per yr
- Extrahepatic syndromes: mixed cryoglobulinemia, porphyria cutanea tarda, lichen planus, leukocytoclastic vasculitis, thyroiditis, MPGN, IPF, NHL, and monoclonal gammopathies
- Serologic, virologic, & genetic tests (screen all adults [✓ anti-HCV] *JAMA* 2020;323:970) anti-HCV (ELISA): ⊕ in 6 wk, does *not* = recovery or immunity; can be ⊖ after recovery HCV RNA: ⊕ w/in 2 wk, marker of active infection HCV genotype (1–6): guides duration & predicts response to Rx; geno. 3 a/w ↑ risk HCC
- Dx: *acute* hepatitis = ⊕ HCV RNA, ± anti-HCV; *resolved* = ⊖ HCV RNA, ± anti-HCV; *chronic* = ⊕ HCV RNA, ⊕ anti-HCV
- Treatment indications (www.hcvguidelines.org) (*Lancet* 2019;393:1453; *Hepatology* 2020;71:686) Acute: if no spont. clearance at 12–16 wk, can Rx w/ same regimens for chronic HCV Chronic: ↓ HCC & mortality. Recommended for all except if ↓ life expectancy.

Recommended First-Line Oral Direct-Acting Antiviral (DAA) Regimens	
Regimen (simplified)	**Indication**
Sofosbuvir & velpatasvir	Genotypes 1–6, 12 weeks Rx
Glecaprevir & pibrentasvir	Genotypes 1–6; 8 weeks Rx
Simplified treatment: adults w/ HCV w/o cirrhosis or w/ compensated cirrhosis & no prior HCV treatment; cannot have HIV, HBsAg ⊕, pregnancy, HCC, ESRD, or liver transplant; if decompensated or previously treated, refer to GI for assistance	

Based on *Hepatology* 2020;71:686. Antiviral classes: RNA *polymerase inhibitor* ("…buvir"); *NS5a inhibitor* ("…asvir"); *NS3/4A protease inhibitor* ("…previr")

- Monitoring on Rx: CBC, INR, LFTs, GFR, HCV VL prior to starting Rx. PIs contraindicated if decomp. liver dx (ascites, encephalopathy) or CPS ≥7. D/c Rx if jaundice, N/V, weakness, 10x ↑ in ALT, or significant ↑ in bili, Aϕ, INR after 4 wks.
- Goal is *sustained virologic response* (SVR) = ⌀ viremia 12 wks after completion of Rx. Success depends on genotype but SVR rates >90% with current regimens.
- Special populations (HCV/HIV coinfection, decompensated cirrhosis, s/p liver transplant, renal impairment): www.hcvguidelines.com for updated recs on mgmt
- Vaccinate all chronic HCV patients against HBV and HAV if not immune
- Postexposure (needlestick risk ~3%) Ppx: none, although sofosbuvir-velpatasvir under investigation in clinical trial; if HCV RNA → ⊕, consider Rx w/in 3 mos

Hepatitis D (RNA; *NEJM* 2023;389:58)

- Transmission: blood or sexual; endemic in Africa & E. Europe. Generally requires HBV infxn in order to cause coinfection or superinfection; in rare cases (immunosupp s/p liver transplant) can replicate autonomously.
- Natural hx: acute HBV–HDV coinfection resolves in >80% of cases; however, acute HDV superinfxn leads to chronic HBV–HDV in most cases (↑ progression to cirrhosis, HCC)
- Dx: ✓ total anti-HDV once in all HBV-infected patients, if antibody ⊕, confirm w/ HDV RNA

Hepatitis E (ssRNA; *World J Gastro* 2016;22:7030; *Gastro Clin N Am* 2017;46:393)

- Most common cause of acute viral hepatitis in endemic areas
- Transmission: fecal–oral; travelers to central & SE Asia, Africa, and Mexico; exposure to swine a/w cases in Europe. Few cases in U.S., but 16% of population have IgG anti-HEV.
- Natural hx: often asx, sometimes causes acute hepatitis w/ ↑ mort. (10–20%) if pregnant; rarely

can become chronic in transplant Pts
- Dx: IgM anti-HEV (through CDC), HEV RNA; treatment is generally supportive only
- Extrahepatic sx: arthritis, pancreatitis, anemia, neuro (GBS, meningoencephalitis)

Other viruses (human pegivirus, CMV, EBV, HSV, VZV)

Autoimmune Hepatitis (AIH)

Classification (*J Hep* 2015;62:S100; *World J Gastro* 2015;21:60)

- Type 1: anti–smooth muscle Ab (ASMA), ANA; anti–soluble liver antigen (anti-SLA), a/w more severe disease and relapsing disease (found in 10–30% Pts), IgG often ↑
- Type 2: anti–liver/kidney microsome 1 (anti-LKM1); anti–liver cytosol type 1 (anti-LC-1)
- Overlap syndrome: AIH + PBC (suspect if ⊕ AMA or ⊕ histology → "autoimmune cholangitis")
- Drug-induced: minocycline, nitrofurantoin, infliximab, hydralazine, α-methyldopa, statins, ICI

Diagnosis and treatment (*J Hepatol* 2015;63:1543; *Clin Liver Dis* 2015;19:57)

- 70% female; bimodal presentation in the second and fifth decades of life
- 40% present w/ severe AIH (3% ALF) w/ ALT >10× ULN; 34–45% asx
- Extrahepatic syndromes: thyroiditis, arthritis, UC, Sjögren's, Coombs ⊕ anemia, celiac
- Dx: scoring system combining serologies, ↑ IgG, ⌀ viral hepatitis, & liver bx (interface hepatitis & lymphoplasmacytic infiltrate) has high Sp & mod Se (*Dig Dis* 2015;33[S2]:53)
- Rx: (1) ALT or AST >10× ULN, (2) IgG >2× ULN + ALT >5× ULN, (3) bridging/multiacinar necrosis, (4) cirrhosis w/ inflammation on bx, (5) AST/ALT >2x ULN + sx
- Induction Rx: (1) prednisone monoRx, (2) prednisone + AZA, or (3) budesonide (if non- cirrhotic) + AZA → 65–80% remission; taper steroids as able; relapse 50–80%
- Nonresponders or AZA intolerant: cyclosporine, tacrolimus, MMF, rituximab, infliximab

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Other Causes of Hepatitis or Hepatotoxicity

Alcohol-associated hepatitis (*J Hepatol* 2019;72:671; *NEJM* 2022;387:2436)

- Sx: progressive jaundice, tender hepatomegaly, fever, ascites, anorexia
- Labs: AST usually <400 w/ AST:ALT > 2:1, ↑ Tbili >~3 & ↑ INR , ↑ WBC
- Prognosis: scoring systems include Maddrey's discriminant fxn (MDF), Lille model, MELD. MDF (4.6 × [PT – control] + Tb) ≥32 w/ 30–50% 1-mo mortality if unRx'd
  - Lille model: score >0.45 after 4 d or 1st week predicts poor response to further glucocorticoid Rx and a/w ↓ in 6-mo survival (*Hep* 2007;45:1348; *Am J Gastro* 2017;112:306)
  - Combination of Lille + MELD scores best predictor of mortality (*Gastro* 2015;149:398)
- Rx: consider if MDF ≥32, MELD >18, or presence of encephalopathy
  - Glucocorticoids (eg, methylprednisolone 32 mg/d or prednisolone 40 mg/d × 4 wk → 4–6 wk taper) may ↓ 1-mo but not 3-mo mortality (*NEJM* 2015;372:1619, CD001511)
  - Contraindic: active GIB, uncontrolled bact/fungal/TB infxn, AKI, untreated HBV
  - Early nutrition consult: goal 35–40 kcal/kg/d & 1.5 g protein/kg/day (*NEJM* 2022;387:2436)
- Consider early transplantation in carefully selected Pts (*Gastro* 2018;155:422)

Acetaminophen hepatotoxicity (*Clin J Transl Hepatol* 2016;4:131; *BMJ* 2016;353:i2579)

- Pathophysiology: >90% of acetaminophen (*N*-acetyl-*p*-aminophenol, APAP) metab into nontoxic metab, but ~5% metab by CYP2E1 into NAPQI, a hepatotoxic metab detoxified by glutathione conjugation; APAP overdose (>10 g) depletes glutathione stores → injury
- CYP2E1 *induced* by fasting, alcohol, and certain anticonvulsants and anti-TB drugs, resulting in injury with even low doses (2–6 g) of acetaminophen

- Liver dysfunction may not be apparent for 2–6 d; nausea, vomiting, & abdominal pain 1st sx
- Rx: NG lavage, activated charcoal if w/in 4 h. Consider early transfer to transplant ctr.
  ***N*-acetylcysteine:** administer up to 72 h after ingestion, if time of ingestion unknown or chronic ingestion >4 g/d; low threshold to start NAC w/ low or undetectable APAP
  PO NAC (preferred): 140 mg/kg loading dose → 70 mg/kg q4h × 17 additional doses

Ischemic hepatitis

- "Shock liver" w/ AST & ALT >1000 + ↑↑ LDH (ALT:LDH ratio often <1:5); delayed ↑↑ Tbili
- Seen in HoTN & CHF; often requires ↑ venous + ↓ portal/arterial pressure + hypoxia

Metabolic-dysfxn-associated steatotic liver disease (MASLD) (*Lancet* 2024;404:1761)

- Definition: fatty infiltration of liver + absence of EtOH or other cause of steatosis (HCV, etc.)
  MASLD = steatosis, ∅ inflam; **MASH** = steatosis + inflam ± fibrosis on bx
- MASLD: 25% of U.S. pop. & over 60% in T2DM & obesity
- MASH: 2–5% of MASLD & risk of cirrhosis in MASH w/ fibrosis on bx is 30% at 10 y
- Clinical: 80% asx, ↑ ALT > AST, but nl ALT/AST does not exclude poss. of MASH on bx
- Dx: liver bx remains gold standard. FIB-4/NAFLD fibrosis score predicts MASH w/ advanced fibrosis w/ PPV >80%; best for excluding advanced fibrosis. Vibration-controlled transient and ultrasound elastography are alternatives (*JAMA 2024;331:1287*).
- Rx: wt loss (≥10%), exercise, DM and lipid control, GLP-1RAs (*NEJM* 2024;391:299 & 2025;NEJMoa2413258), bariatric surgery (*Lancet* 2023;401:1786); resmetirom (activates THRβ) (*NEJM* 2024;390:497). Lanifibranor (PPAR agonist) and THRβ agonist + FGF21 analog under study (*NEJM* 2021;385:1547 & 2024;389:998 & 390:497).
- HCC a complication of MASLD, usually in setting of MASH cirrhosis

ACUTE LIVER FAILURE (ALF)

Definition (*Am J Hepatol* 2023;118:1128)

- Acute liver injury (<26 wks) + coagulopathy + encephalopathy w/o preexisting liver disease except autoimmune hepatitis, Budd–Chiari, Wilson disease
- Fulminant if encephalopathy <8 wks from jaundice onset, subfulminant if 8–26 wks
- Acute-on-chronic liver failure: acute insult to liver in Pt w/ underlying chronic liver disease

Etiology (*J Hepatol* 2015;62:S112)

- **Drugs/toxins** (nearly 80% of cases in U.S.; *Gastro* 2015;148:1353; *Clin Liver Dis* 2017;21:151)
  Dose-dependent: acetaminophen (most common cause; >40% of cases in U.S.)
  Idiosyncratic, not dose related: anti-TB drugs (INH, RIF, PZA); AEDs (phenytoin, valproate, carbamazepine); NSAIDs; abx (eg, fluoroquinolones, macrolides, nitro- furantoin); drugs of abuse (MDMA & cocaine); others (amiodarone, TCAs)
  Toxins: *Amanita phalloides* (mushroom sp. in West Coast), certain herbal preparations
- **Viral**: HAV, HBV, HCV (rare), HDV + HBV, HEV (esp. if pregnant). In immunosupp: HSV (50% have skin lesions), EBV, VZV, CMV, HHV6.
- **Vascular:** Budd–Chiari, ischemic hepatitis, hepatic sinusoidal obstruction syndrome
- **Other:** Wilson disease, pregnancy-related ALF (acute fatty liver, preeclampsia, HELLP), initial presentation of autoimmune hepatitis; idiopathic

Clinical manifestations (*Lancet* 2024;404:789)

- Initial presentation: N/V, malaise, RUQ pain, jaundice, encephalopathy, multiorgan failure
- Neurologic: **encephalopathy:** grade 1 = attn deficit, disordered sleep; grade 2 = *asterixis*, Δ MS; grade 3 = somnolence, rigidity; grade 4 = coma; ↑ ICP w/ bradycardia & HTN (Cushing reflex); **cerebral edema:** astrocyte swelling related in part to ↑ NH_3 levels
- Cardiovascular: **hypotension** with low SVR, shock
- Pulmonary: **respiratory alkalosis**, impaired peripheral O_2 uptake, pulm edema, ARDS
- GI: bleed common (need PPI Ppx), pancreatitis (due to ischemia, drugs, infxn)
- Renal: ATN, **hepatorenal syndrome**, hyponatremia, hypokalemia, hypophosphatemia
- Hematology: **bleeding diathesis** w/ thrombocytopenia, ↑ PT/PTT, ↓ fibrinogen, ↓ synthesis of coag factors balanced by ↓ protein C/S; bleeding mostly due to low plts, DIC
- **Infection**: espec. with *Staph*, *Strep*, GNRs, and fungi (↓ immune fxn, invasive procedures); *fever and ↑ WBC may be absent, most common sites are respiratory, urinary, & blood*
- Endocrine: **hypoglycemia** (↓ glc synthesis), metabolic acidosis (↑ lactate), adrenal insuf.

Workup (*Clin Liver Dis* 2017;21:769)

- CBC, PT/PTT, LFTs, lytes, BUN/Cr, NH_3, pH, *arterial* lactate, acetaminophen level, HIV, amylase/lipase, viral serologies (qv) in all, with additional labs as below if suspected
- Autoimmune hep serologies & IgG levels, ceruloplasmin & serum/urine copper, preg test
- Imaging studies (RUQ U/S or abd CT, Doppler studies of portal and hepatic veins)
- Liver biopsy if underlying etiology remains elusive after initial testing

Management (*J Clin Exp Hepatol* 2015;5:S104; *Am J Gastro* 2023;118:1129)

- **ICU care at liver transplant center** for hemodynamic & ventilatory support; CVVH for AKI
- Early listing for liver transplantation in selected Pts (vide infra)
- Cerebral edema: consider ICP monitoring if grade 3/4 enceph; if ↑ ICP → mannitol 0.5–1.0 mg/kg; if arterial NH_3 >150, grade 3/4 enceph, AKI or on vasopressors → prophylactic 3% saline with goal Na 145–155 mEq/L; barbiturates & hypothermia if refractory ↑ ICP
- Encephalopathy: intubate for grade 3 or 4; lactulose is of little benefit & may be detrimental
- Coagulopathy: vit K, FFP/plts/cryo only if active bleeding (↑ risk of volume overload)
- Infection: low threshold for abx (broad spectrum, eg, vancomycin & 3rd-gen ceph.) if suspect infection; antifungal coverage in high-risk Pts (TPN, CVVH)
- Rx of specific causes: NAC if acetaminophen; antiviral for HBV; plasma exchange can be temporizing measure for Wilson disease; IV acyclovir for HSV; PCN-G for *A. phalloides;* delivery of child for pregnancy-related; TIPS, anticoag for Budd–Chiari. Lack of data for use of steroids in autoimmune ALF, but often given (*Hepatology* 2014;59:612).
- NAC improves survival in non-APAP ALF (*Ann Gastro* 2021;34:235)
- King's College Criteria for Liver Transplantation consideration:
  - Acetaminophen ALF: arterial pH <7.30 or Grade III/IV enceph + INR >6.5 + Cr >3.4
  - Non-acetaminophen ALF: PT >100 or any 3: age <10 or >40 y, jaundice >7 d prior to onset of encephalopathy, PT >50 or INR >3.5, Tbili >18, unfavorable disease (viral hepatitis, DILI, Wilson disease, or low factor V level)

Prognosis (*Ann Intern Med* 2016;164:724; *World J Gastro* 2016;22:1523)

- Non-acetaminophen ALF mortality ~70%, acetaminophen-induced ALF mortality ~25–30%
- HBV, Wilson, AIH, DILI, Budd–Chiari ~ associated with ↓ prognosis
- Factor V level <20% in Pts <30 yrs or <30% in >30 yrs associated w/ poor prognosis

CIRRHOSIS

Definition (*Dig Dis* 2016;34:374; *NEJM* 2016;375:767; *J Hep* 2021;74:1014)

- Definition **fibrosis & regenerative nodules** causing distortion of hepatic vascular architecture resulting in elevated portal pressure
- **Decompensated** = complication due to ↑ portal pressure such as: variceal bleed, ascites, or hepatic encephalopathy

Etiologies

- **Alcohol**, toxins (eg, arsenic)
- **Metab. dysfxn-assoc. steatotic liver dis. (MASLD)**; cause of most "cryptogenic cirrhosis"
- **Viral hepatitis**: chronic HBV, HCV, HDV infection
- **Autoimmune hepatitis:** ♀, ↑ IgG, ⊕ ANA, ASMA, anti-LKM-1, anti-LC1
- **Metabolic diseases**: hemochromatosis, Wilson disease, α_1-AT deficiency, celiac dis
- **Biliary tract diseases**: primary biliary cholangitis, secondary biliary cirrhosis (calculus, neoplasm, stricture, biliary atresia), primary sclerosing cholangitis
- **Vascular diseases:** Budd–Chiari syndrome, R-sided CHF, constrictive pericarditis, SOS
- **Medications:** amiodarone, methotrexate, vitamin A, valproic acid, isoniazid

Clinical manifestations

- Nonspecific sx (anorexia, fatigue) or jaundice, encephalopathy, ascites, variceal bleeding

Physical exam

- Liver: *initially* enlarged, palpable (L lobe predom), firm; *eventually* shrunken, nodular
- Signs of liver failure: jaundice (bili >2.5), spider angiomata & palmar erythema (↑ estradiol), Dupuytren contractures, white nail lines (Muehrcke lines) & proximal nail beds (Terry nails), ↑ parotid & lacrimal glands, gynecomastia, testicular atrophy, asterixis, encephalopathy, clubbing, hypertrophic osteoarthropathy, anovulation in women
- Signs of portal HTN: splenomegaly, ascites, dilated superficial abd veins (caput medusae), epigastric Cruveilhier–Baumgarten venous hum (flow through recanalized umbilical vein)

Laboratory studies (*JAMA* 2023;329:1589)

- LFTs: ↑ **bili**, ↑ **PT/INR** (poor correlation w/ bleeding risk; factor VIII nl b/c not synthesized by liver), ↓ **alb**, ± ↑ aminotransferases (AST > ALT if late) and ↑ Aϕ (variable)
- Hematologic tests: anemia (marrow suppress., hypersplenism, Fe ± folate defic.), neutro-penia (hypersplenism), thrombocytopenia (hypersplenism, ↓ Tpo, EtOH tox)
- Chem: ↓ Na (↑ ADH due to ↓ EAV); ↑ Fe/TIBC, ↑ ferritin (released from hepatocytes)
- Lab indices predictive of cirrhosis: AST/plt >2; Lok index; Bonacini score (*JAMA* 2012;307:832)
- Indirect markers of fibrosis: FibroTest/FibroSURE, Hepascore (good at identifying significant fibrosis F2–F4), FIB-4 index (NAFLD, HCV), NAFLD fibrosis score, APRI (HCV), noninvasive imaging (eg, U/S or MR elastography)

Workup (*Am J Gastro* 2017;112:18; *Lancet* 2021;398:1359)

- Abd **U/S w/ Doppler:** liver size & echotexture, r/o HCC, ascites, ✓ patency of vasculature
- Determine etiology: hepatitis serologies (HBsAg, anti-HBs, anti-HCV), autoimmune hepatitis studies (IgG, ANA, ASMA), Fe and Cu studies, α_1-AT, AMA, IgA TTG Ab
- Assess fibrosis: biomarkers (FibroSURE = panel of 5 markers validated in HCV, ↑ score predictive of fibrosis); elastography (U/S or MR-based; measurement of liver stiffness)
- Liver bx (gold standard): percutaneous or transjugular (consider if ascites or coagulopathy), used to confirm presence of cirrhosis and etiology, not always needed

Prognosis (www.mdcalc.com/child-pugh-score-cirrhosis-mortality)

- **Modified Child-Turcotte-Pugh (CPS)** score based on ascites, enceph., & labs (bili, alb & INR; see Appendix). CPS A (5–6 pts): 1-y survival 100%, B (7–9): 80%; C (10–15): 45%.
- **MELD-Na or 3.0** (**M**odel for **E**nd-Stage **L**iver **D**isease; *Gastro* 2021;161:1887): used to stratify liver txp list & predict 3-mo survival in cirrhosis and some acute forms of liver dis. Based on sex, serum albumin, Cr, INR, total bili, Na. Calculator: https://optn.transplant.hrsa.gov/resources/allocation-calculators/meld-calculator/. If MELD <21, additional predictors of mortality include refractory ascites, ↑ HVPG & ↓ QoL

Ascites (see "Ascites" for diagnostic eval; *Dig Dis* 2017;35:402; *Hepatology* 2021;74:1014)

- Due to portal HTN (defined as hepatic venous pressure gradient [HVPG] >5 mmHg)
- Develops in 60% w/in 10 y; often first decompensating event
- Treatment: ↓ **Na intake** (1–2 g/d); restrict intake of free water if Na <125
  - **Diuretics:** goal diurese ~1 L/d. Use spironolactone ± furosemide in 5:2 ratio (uptitrate as able); urine Na/K >1 implies effective natriuresis if Pt compliant w/ low-Na diet.
  - Avoid NSAIDs/ACEI/ARBs in cirrhosis because they interfere w/ diuretic action
  - Long-term albumin infusions ↓ mortality (*Lancet* 2018;391:2417), but not widely adopted
- **Refractory ascites:** seen in 5–10% of Pts; 2-y survival 25%
  - Defined as diuretic-resistant if on 2-g Na diet w/ minimal weight loss on max diuretics, or diuretic-induced complications (AKI, Na <125, ↑ K, encephalopathy)
  - Conflicting evid. for d/c'ing βB (*Hep* 2016;63:1968; *J Hepatol* 2016;64:574). Discontinue if SBP <90 or MAP ≤82 mmHg, serum Na <120 mEq/L, AKI, HRS, SBP, sepsis, severe alcohol-assoc hepatitis, or poor follow-up. If limited by HoTN, can add midodrine.
  - **Large-volume para** (LVP; >5 L fluid removal): give 6–8 g albumin per L fluid removed (above 5 L) as colloid replacement a/w ↓ risk of post-para circulatory dysfxn & possibly ↓ mort. (*Hep* 2012;55:1172). Avoid LVP if SBP present because ↑ risk of AKI.
  - **Transjugular intrahepatic portosystemic shunt** (TIPS) (*Gastro* 2017;152:157) ↓ ascites in 75%; ↑ CrCl, ↑ enceph, survival benefit over LVP remains controversial Contraindic: grade II enceph, CHF or pulm HTN, active infxn or biliary obstruction Complications: bleeding, fistula; stent thrombosis (1-y patency w/ coated stents ~80%); infxn ("endotipsitis"); new or ↑ enceph in 20–30% (*Am J Gastro* 2016;111:523), hemolysis Consider liver transplant if above fail
- **Hepatic hydrothorax:** 2° diaphragmatic defect; often unilateral, R > L, ± ascites
  - Treatment: avoid chest tube (↑ complications); Rx same as ascites (TIPS if refractory). Indwelling pleural catheter potential option if refractory for palliation (*Chest* 2019;155:307).

Spontaneous bacterial peritonitis (SBP; see "Ascites"; *Hepatology* 2021;74:1014)

- High mortality rate; risk factors include ascitic TP <1 g/dL, hx of SBP, current GIB
- Can p/w encephalopathy, abd pain, fever, *but often* (*25%*) *asx;* perform diagnostic paracentesis in all hospitalized patients with cirrhosis and ascites
- Micro: typically, monobacterial GNRs (*E. coli, Klebs*) > GPCs (*S. pneumo, enterococcus*)
- Rx: 3rd-gen. ceph 1st line; consider pip/tazo or mero if ↑ risk of MDRO; vanc if prior MRSA ⊕; IV albumin 1.5 g/kg at time of dx & 1 g/kg on day 3 → ↑ survival in those w/ renal dsyfxn or hepatic decompensation (*NEJM* 1999;341:403; *Hepatology* 2021;74:1014)
- If not clinically improving, repeat para at 48 hrs. Expect 25% ↓ in PMNs if Rx working.
- Indefinite Ppx if (1) h/o SBP or (2) ascitic TP <1.5 plus: Na ≤130 or Cr ≥1.2 or BUN ≥25 or [CPS ≥9 + Tbili ≥3] → cipro 500 mg qd or Bactrim DS qd. Short-term Ppx: CTX 1 g IV × 5 d if GIB (Δ to cipro 500 bid/Bactrim DS bid when eating).

Gastroesophageal varices ± UGIB (see also "GIB"; *Hepatology* 2024;79:1180)

- Presence of varices correlates w/ severity of liver dis (40% of Child A Pts → 85% Child C)
- ↑ varix size, child B/C, & red wale marks assoc w/ ↑ risk of bleeding
- UGIB 1° prevention: screen at time of dx w/ EGD; data best for Pts w/ med–large varices
  - **Nonselective β-blockers** (*Ann Gastro 2*019;32:287): ~50% ↓ risk of bleeding & ↓ mortality if med–large varices. Carvedilol preferred over nadolol or propranolol as ↓ MAP & HVPG more;

delays progression of varices (*Gut* 2017;66:1838). Titrate to max tolerated dose; EGD not req. to document improvement. SBP should be maintained ≥90 mmHg.

Endoscopic variceal ligation (EVL): superior to βB in ↓ risk of 1st bleed but no diff in mortality (*Ann Hep* 2012;11:369); risk of serious complications (esoph perf, ulcers). Repeat q1–4wk until varices gone, w/ f/u EGD at 3 mo then q6–12mo.

βB vs. EVL: choice based on Pt/MD preference; βB often 1st for small varices; larger varices may benefit more from EVL; combo for 1° Ppx currently not recommended

- 2° prevention: for all Pts after 1st bleed, given ~50% risk of rebleed & ~30% mortality; βB + EVL > either alone; TIPS if refractory, or consider in child B/C w/in 72 h of admission for EV bleed (↓ rebleeding, ↑ enceph., ∅ Δ mort.) (*Hepatology* 2017;65:310)

Hepatic encephalopathy (HE) (*NEJM* 2016;375:1660; *Hepatology* 2014;60:715)

- Pathogenesis: failure of liver to detoxify NH_3 + other substances (eg, ADMA) that cause cerebral edema, ↓ O_2 consumption, ↑ ROS → brain dysfxn
- Precipitants: bleeding, infxn, med nonadherence, ↓ K, ↓ Na, dehydration, hypoxia, portosystemic shunt (eg, TIPS), meds (eg, sedatives), acute insult to liver (eg, PVT)
- Stages: see “Acute Liver Failure”
- Dx: serum NH_3 levels have poor Se for dx & monitoring Rx; remains a *clinical dx*
- Rx: identify/correct precipitants; **lactulose** (acidification of colon: NH_3 → NH_4^+) w/ goal 2–4 stools/d (PEG also effective; *JAMA IM* 2014;174:1727). Add **rifaximin** 550 mg bid (↓ gut bacteria → ↓ NH_3 prod) if refractory, after 2nd recurrence on lactulose, or after TIPS (*Annals* 2021;174:633). Rarely, oral branched-chain AAs, oral L-ornithine-L-aspartate, and probiotics. Maintain K >4, avoid alkalosis as able.

Hepatorenal syndrome (HRS) (*Hepatology* 2021;74:1014; *Gastro* 2024;166:202)

- ↓ renal blood flow due to renal vasoconstriction from sympathetic, RAAS, and vasopressin
- Criteria: (1) cirrhosis w/ ascites; (2) **acute kidney injury** (serum Cr ↑ ≥0.3 mg/dL w/in 48 h or ≥50% ↑ in serum Cr from baseline; *Gut* 2015;64:531); (3) ∅ improvement in Cr after d/c diuretic & volume expansion (1 g/kg/d of albumin × 2 d); (4) ∅ shock (prerenal azotemia/ATN); (5) ∅ nephrotoxic meds; (6) ∅ intrinsic kidney disease

  HRS-AKI: development in <2 wk; usually occurs in severe liver failure, often following precipitating event (see later); median survival 2 wk

  HRS-CKD: more indolent, median survival 6 mo; liver failure present < than in HRS-AKI
- Precipitants: GIB, overdiuresis, infection, serial LVP, drugs (aminoglycosides, NSAIDs)
- Rx: *if critically ill* → terlipressin (or other vasopressor [eg, norepi or vaso]) + albumin (*NEJM* 2021;384:818) to ↑ MAP 10 mmHg. *If not critically ill* → octreotide (100–200 μg SC tid) + midodrine (max 15 mg PO tid) + 1 g/kg (max 100 g) albumin on day of presentation → 20–60 g albumin qd to ↑ MAP. May need dialysis or TIPS as bridge to liver txp.

Hepatocellular carcinoma (HCC; qv in Heme-Onc) (*Nat Rev* 2021;7:6)

- ↑ risk w/ cirrhosis of any type (leading cause of death in cirrhosis, 1–6%/y) but esp. ↑ w/ viral (Hep B/C~3–8%/y), concom. EtOH, obesity-related MASH, HFE, DM, or tobacco
- Clinical: asx vs. hepatic decompensation (eg, ascites, HE), PVT w/ tumor thrombus
- Dx: screen Pts w/ cirrhosis q6mo w/ U/S ± AFP; alternative is dual-phase CT/MRI
- Rx: see “HCC” in Heme-Onc

Other complications

- **Hepatopulmonary syndrome** (HPS) (*Dig Dis Sci* 2015;60:1914; *Hepatology* 2021;74:1014)

  Abnl gas exchange (A-a gradient ≥15 or P_aO_2 <80) caused by intrapulmonary vascular dilatations leading to intrapulmonary shunting (improves with O_2)

S/S: platypnea-orthodeoxia (dyspnea & hypoxia w/ sitting up), clubbing, spider angiomas
Dx w/ contrast echo showing "late" A-V shunting (contrast in LA 3–6 cycles after RA).
Macroaggregated albumin lung perfusion scan (^{99m}Tc-MAA) is less Se alternative.
Rx: O_2; potential embolization if large vessel on CT, TIPS; liver txp only definitive Rx

- **Portopulmonary hypertension** (POPH) (*Expert Rev Gastro Hepatol* 2015;9:983)
  Pulm HTN in Pt w/ portal HTN w/o other cause. ESLD→ ↑ endothelin→ pulm vasoconst.
  Rx w/ same therapies as for idiopathic PAH, incl prostacyclin analogs, endothelin receptor antagonists, sildenafil; liver transplant is often curative
- **Acute-on-chronic liver failure:** decompensation triggered by precip. (eg, infxn, EtOH)
- **Cirrhotic cardiomyopathy:** ↓ inotropic & chronotropic response, ↓ systolic & diastolic fxn, ↑ QT, hyperkinetic circulation, high output; ↑ troponin & BNP
- **Infxns:** unless immune, vaccinate for HAV, HBV, PCV13, PPSV23, COVID-19; flu yearly. Cellulitis in ~20% of Pts hospitalized w/ cirrhosis, often in abd or LE a/w edema.
- **Endocrine:** diabetes (15–30%), ↑ frequency of adrenal insuffic. (*Dig Dis Sci* 2017;62:1067)
- **Coagulopathy:** balanced defects w/ ↓ synth of coag factors, hyperfibrinolysis, ↓ plt balanced by ↓ synthesis anticoag factors (protein C/S), defic. of profibrinolytic factors, ↑ levels of vWF. No support for routine FFP, plt, or cryo unless DIC.
- **Nutrition:** monitor and supplement fat-soluble vitamins, zinc, screen for malnutrition, sarcopenia & frailty; ensure protein intake 1.2–1.5 g/kg/d (*Hepatology* 2021;74:1611)
- Meds: limit acetaminophen ≤2 g/d; avoid ASA/NSAIDs; aminoglycosides contraindicated

Liver transplantation (*NEJM* 2022;389:1888)

- Undertake evaluation when MELD ≥15. Exception points added if HCC, HPS, others (eg, cholangiocarcinoma, CF, TTR amyloidosis).
- Indic: recurrent/severe enceph, refractory ascites, recurrent variceal bleeding, HRS, HPS, PPH, HCC (if no single lesion is >5 cm *or* ≤3 lesions with largest ≤3 cm), ALF
- Contraindic: inadequate social support, active substance abuse (some exception), sepsis, advanced cardiopulm dis., extrahepatic Ca, cholangio Ca, hemangiosarcoma, persistent noncompliance, AIDS, ALF w/ sustained ICP >50 mmHg or CPP <40 mmHg
- Survival: 1-y up to 90%, 5-y up to 80%; autoimmune liver disease, such as AIH/PBC/PSC may recur in 10–30% (or more) of allografts

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Other Etiologies of Cirrhosis

Hemochromatosis & iron overload syndromes (*NEJM* 2022;387:2159)

- Recessive disorder of iron sensing or transport leading to tissue **iron deposition**
- **HFE** mutations (85% of cases): typically C282Y homozyg. (~0.5% of N. Europeans), rarely C282Y/H63D compound heterozyg. C282Y homozygotes: 28% of ♂ & 1% of ♀ develop iron overload; sx delayed in ♀ due to menses ↓ Fe load. C282Y/H63D: only 1.5% manifest iron overload.
- Non-HFE mutations: hemojuvelin, hepcidin, transferrin receptor 2, & ferroportin
- 2° causes of iron overload: iron-loading anemias (eg, thalassemia major, sideroblastic anemia, aplastic anemia), parenteral iron overload (RBC transfusions, long-term HD), chronic liver disease (due to EtOH, HBV, HCV, MASH, etc.), dietary iron overload
- Sx: fatigue & arthralgias, loss of libido in ♂. In *advanced disease* (rare): bronze skin (melanin + iron), hypogonadism (esp. in juvenile onset), DM, arthropathy (MCP), CHF, infxns (↑ risk *Vibrio*, *Listeria*, *Yersinia*), cirrhosis (↑ risk if EtOH/fatty liver disease; 15% risk of HCC). Disease also a/w ALS (H63D homozygotes) & porphyria.
- Dx: iron sat >45% (iron/TIBC × 100%); ↑ ferritin (acute-phase reactant, so poor Sp; often nl in young). If ↑ iron sat. → ✓ HFE to confirm dx, imaging by MRI (black liver). If HFE ⊕ & ferritin >1000 ng/mL or ↑ LFTs → liver bx for quant Fe index & to stage fibrosis.
- Treatment: phlebotomy (250 mL = 1 unit, ~250 mg of Fe) qwk until Fe sat <50% & ferritin 50–100 µg/L, then q3–4mo; PPI ↓ intestinal Fe absorption & may ↓ need for phleb.; avoid vit C &

uncooked seafood; deferoxamine if phleb. contraindic.; genetic counseling

Wilson disease (*NEJM* 2023;389:922)

- Recessive disorder of copper transport (mutation in *ATP7B*) → **copper overload**
- Epidemiology: 1 in ~30000 w/ age of presentation generally ranging from 3 to 55 y
- Extrahepatic: neuro ψ, parkinsonism, movement abnl (hepatolenticular), Kayser–Fleischer rings (⊕ in 99% w/ neuro ψ, but in <50% w/o), Coombs ⊖ hemolytic anemia, renal
- Dx: ↑ 24-h urine Cu, ↓ serum ceruloplasmin (Se 90%), liver bx w/ hepatic Cu content, genetic testing for *ATP7B* gene helpful if unclear dx. In *acute liver failure*, Aϕ/bili <4 + AST/ALT >2.2 better Se & Sp than urine Cu or ceruloplasmin (*Hepatology* 2008;4:1167).
- Treatment: **chelation** w/ D-penicillamine (supplement B6 as D-pen inactivates); alternative is trientine (↓ toxicity w/ ≈ efficacy, but $$). **Zinc:** ↓ intestinal Cu transport & can help delay disease; best used in conjunction w/ chelation (give 5 h after chelators). Eliminate Cu-rich foods. Transplant for ALF or unresponsive to Rx. Investigational: bis-choline tetrathiomolybdate may ↓ neurologic deterioration compared to trientine.

α_1-Antitrypsin deficiency (α_1-AT) (*J Hepatol* 2016;65:413; *NEJM* 2020;382:1443)

- Abnl α_1-AT → polymerization in liver (cirrhosis) & uninhibited protease activity in lung (emphysema). Affects 1/3000 of European ancestry. Varied presentations: neonatal hepatitis; cholestatic jaundice in children; ↑ AST/ALT or cirrhosis in children/adults.
- Extrahepatic disease: panlobular emphysema, necrotizing panniculitis, ANCA vasculitis
- Dx: serum α_1-AT (acute-phase reactant) w/ CRP level (to ensure not ↑ due to inflamm.) gold standard = phenotyping of protease inhibitor (Pi). Alleles most a/w hepatic dis.: Z (63% of ZZ adults have chronic liver dis. and liver fibrosis may be present in 35% of ZZ individuals w/o overt liver disease) & rarely SZ heterozygotes and those with M-Malton (*J Hepatol* 2018;69:1357). Liver bx: characteristic PAS ⊕ cytoplasmic inclusion bodies.
- Rx: avoid EtOH, maintain nl BMI; liver txp if severe; anti-AAT under study (*NEJM* 2022;387:514)

Primary biliary cholangitis (PBC) (*Lancet* 2024;404:1053)

- Autoimmune destruction of *intrahepatic* bile ducts
- Epi: ♀ 40–60 y; a/w Sjögren's (50%), Raynaud's, scleroderma, celiac & thyroid disease; may be triggered by infxn or toxin; a/w X monosomy, variants in IL-12α & IL-12R genes
- Sx: fatigue/sleep disturbance, pruritus, jaundice, 50% asx w/ only LFT abnormalities
- Ddx: PSC, AIH, hepatic sarcoidosis, meds, idiopathic adult ductopenia, biliary stricture/Ca
- Dx: ↑ Aϕ, ↑ bili, ↑ IgM, ↑ chol (mainly HDL-C), ⊕ (AMA) in 95%. If ⊕ AMA, liver bx not needed due to high Se & Sp. 0.5% gen pop ⊕ AMA & nl LFTs → 10% develop PBC at 6 y. If AMA ⊖, liver bx (Pts often ⊕ ANA, smooth muscle Ab; same prognosis as ⊕ AMA).
- Rx: **ursodeoxycholic acid** (UDCA) (13–15 mg/kg bid), monitor for 3–6 mos → ~25% complete response, ↑ survival & ↓ histologic change & ↓ complications (varices).
- Biochemical response predicts clinical outcome.
  - **PPAR agonists** elafibranor (α & δ) or seladelpar (δ) used in combo w/ UDCA or as mono-Rx if cannot tolerate UDCA or if no Δ w/ UDCA after 1 y. Cannot use in decompen cirrhosis. ↓ Aϕ. GI upset w/ elafibranor (*NEJM* 2024;390:783 & 795). Obeticholic acid (FXR agonist) falling out of favor; ↑ pruritus.

  Bezafibrate (fenofibrate similar?) 2nd-line agent in combo w/ UDCA if inadeq. response
  Pruritus: cholestyramine (give 2–4 h after UDCA); if refractory: naltrexone, rifampin, pheresis
  If ESLD: liver tx; ~20% recur but no impact on long-term survival

Primary sclerosing cholangitis (PSC) (*NEJM* 2016;375:1161; *Clin Liver Dis* 2020;15:125)

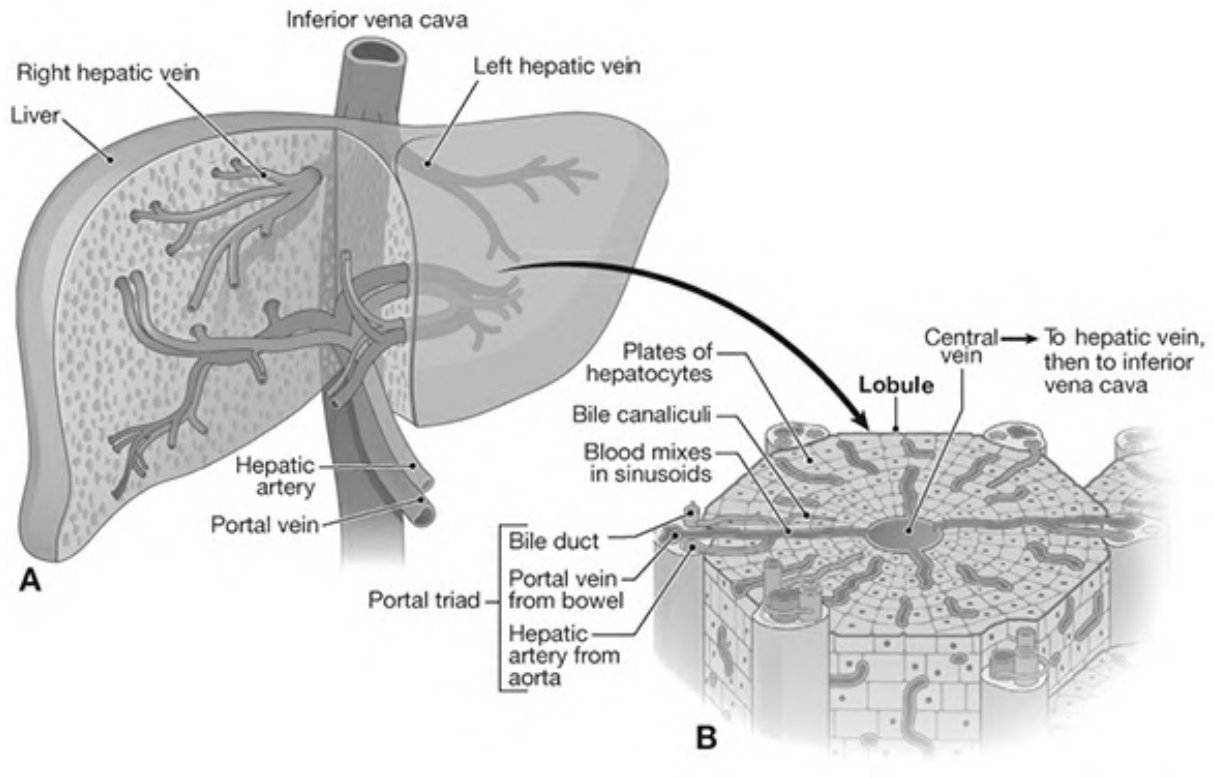
- Diffuse inflammation of *intrahepatic and extrahepatic* bile ducts leading to fibrosis & stricturing of biliary system. A/w HLA-B8 and -DR3 or -DR4, frequent ⊕ autoAb.
- Epi: ♂ > ♀ (20–50 y) ~70% Pts w/ PSC have IBD (usually UC); 1–4% w/ UC have PSC. ⊕

prognostic factors: ♂, absence of IBD, small duct PSC (*Gastro* 2017;152:1829).

- Symptoms: fatigue, pruritus, jaundice, fevers, RUQ pain, IBD; 50% of Pts asymptomatic
- Ddx: extrahepatic obstruction, PBC, overlap w/ AIH, IgG4 autoimmune cholangitis, etc.
- Dx: cholangiography (MRCP ± ERCP) → *multifocal beaded bile duct strictures*; exclude 2° cause; may miss dx if confined to small intrahepatic ducts ("small duct PSC").
  Liver bx if unclear: "onion-skin" fibrosis around bile ducts + some findings similar to PBC.
- Treatment: supportive care, fat-soluble vitamins; no meds have improved survival
  UDCA may ↓ Aϕ & improve Sx, but unclear if beneficial
  If dominant stricture → endoscopic dilation, stenting, or surgical resection
  Cholangiocarcinoma: 15% lifetime risk; annual surveillance w/ MRCP or U/S & CA19-9
  Liver transplantation: ~30% recurrence, though if UC, colectomy may ↓ recurrence

HEPATIC VASCULAR DISEASE

Figure 3-5 Normal hepatic vasculature



(Modified from *The Nature of Disease Pathology for the Health Professions*, 2007; *Hepatology* 2009;49:1729)

Portal vein thrombosis (PVT) (*Gastro* 2025;168:396)

- Definition: thrombosis of portal vein often w/ extension into mesenteric vein/splenic vein
- Etiologies: commonly due to cirrhosis or hypercoagulable state (cancer, infection, OCP, collagen vascular diseases, Behçet's, IBD, surgery, trauma, OCPs, preg)
- Clinical manifestations
  acute: abd pain, distention, fever, hepatic decompen., or asx w/ incidental finding on U/S or CT. If mesenteric vein involved may p/w intestinal infarct. If fever, consider pylephlebitis.

chronic: asx/incidental finding; may p/w s/s of **portal HTN** → hematemesis 2° variceal bleeding, splenomegaly, encephalopathy; ascites uncommon unless cirrhosis

- Dx: LFTs usually nl; begin w/ U/S w/ Doppler, confirm w/ MRA or CT (I^+), angio; consider hypercoag w/u if no obvious etiology. "Portal cavernoma": network of hepatopetal collaterals in chronic PVT—can rarely cause biliary obstruction = portal cholangiopathy.
- Treatment: **Acute:** If noncirrhotic, LMWH → warfarin or DOAC × 6 mo, or indefinitely if irreversible cause. If cirrhotic, anticoag w/ LMWH or UFH is recommended for acute complete main PVT or extens. of PVT into mesenteric veins. Must weigh risk of bleeding. Screen for high-risk varices prior to Rx. **Chronic:** anticoag if noncirrhotic or hypercoag state. If cirrhotic, consider liver txp if sx or progression. In all, screen for varices; if present, variceal bleed Ppx with NSBB prior to anticoag.

Splenic vein thrombosis

- Can occur 2/2 local inflam. (eg, panc.). If p/w bleeding gastric varices → splenectomy

Budd–Chiari syndrome (*NEJM* 2023;388:1307)

- Hepatic outflow obstruction 2/2 occlusion of hepatic vein(s) or IVC → sinusoidal congestion and portal HTN. Can be 1° (eg, thrombosis) or 2° (eg, extravascular compression).
- Etiol.: ~50% due to myeloprolif. d/o a/w *JAK2* mutations (*P. vera*, etc.), hypercoag states (systemic, OCP, pregnancy), tumor invasion (HCC, renal, adrenal), trauma, idiopathic
- Symptoms: hepatomegaly, RUQ pain, ascites, dilated venous collaterals, acute liver failure
- Dx: ± ↑ AST, ALT, & Aϕ; Doppler U/S of hepatic veins (85% Se & Sp); CT (I^+) or MRI/MRV → vein occlusion or ↑ caudate lobe (separate venous drainage); hepatic venography gold standard w/ "spider web" pattern + assess venous pressure; biopsy only if unclear
- Treatment: Rx underlying condition, anticoag (LMWH → warfarin); consider thrombolysis if acute; angioplasty & stent if short stenosis; consider TIPS or DIPS (U/S-guided direct intrahepatic portosystemic shunt) (if other methods fail to treat sx of portal HTN); liver transplant if ALF or failed other options

Sinusoidal obstruction syndrome (SOS) (*Bone Marrow Transplant* 2020;55:485)

- Occlusion of hepatic venules & sinusoids (formerly veno-occlusive disease) 2/2 toxic insult
- Etiologies: post-HSCT (15%), chemo (cyclophosphamide, cytarabine), XRT, bush tea
- Clinical manifestations: painful hepatomegaly, RUQ pain, ascites, weight gain, ↑ bilirubin
- Dx: U/S w/ reversal of portal flow; dx made clinically (early weight gain, ↓ plt refractory to transfusion, ↑ bili, hx of recent toxins); if necessary, liver bx or HVPG (>10 mmHg)
- Rx: supportive, diuretics; if severe → early defibrotide ↑ survival, but side effects & expensive
- Ppx: defibrotide; ursodeoxycholic acid for high-risk HSCT pop; ? use of low-dose heparin

ASCITES

Pathophysiology (*Hepatology* 2021;74:1014)

- Portal HTN → ↑ NO & prostaglandins → splanchnic vasodilatation → ↓ effective arterial volume → ↑ RAAS & ADH → renal Na & H_2O retention → volume overload and ascites
- In malignant or inflammatory ascites, leaking of proteinaceous material occurs from tumor or from inflamed/infected/ruptured intra-abdominal structures

Symptoms

- ↑ abd girth, wt gain, new abd hernia, abd pain, dyspnea, nausea, early satiety

Evaluation (*World J Hepatol* 2013;5:251; *JAMA* 2016;316:340)

- Physical exam: **flank dullness** (>1500 mL needed, Se 80%), shifting dullness (Se ~75%)
- Radiologic: **U/S** detects >100 mL fluid; MRI/CT (also help with Ddx)
- **Paracentesis**: perform in all Pts w/ new ascites, suggested in all hosp. Pts w/ cirrhosis + ascites. Low complic. rate (~1% hematoma). Prophylactic FFP or plts does *not* ↓ bleeding complic. Most useful tests: cell count, alb, total protein (for SAAG), & cx.
- **Serum-ascites albumin gradient (SAAG):** serum alb (g/dL)–ascites alb (g/dL)
  SAAG ≥1.1 diagnoses portal HTN with ~97% accuracy (*Ann Intern Med* 1992;117:215)
  If portal HTN + another cause (seen in ~5% of cases) SAAG still ≥1.1

Etiologies	
Portal HTN Related (SAAG ≥1.1)	**Non-Portal HTN Related (SAAG <1.1)**
Presinusoidal obstruction: portal or splenic vein thrombosis, schisto- somiasis, sarcoidosis, rarely early PBC *Sinusoidal* obstruction: **cirrhosis**, acute hepatitis (including EtOH), malignancy (HCC or mets) *Postsinusoidal* obstruction: right-sided **CHF** (eg, constriction, TR), Budd–Chiari syndrome, SOS	Malig: **peritoneal carcinomatosis**; chylous ascites from malignant lymphoma (↑ TG); Meigs syndrome (ovarian tumor) Infection: TB, chlamydia/gonorrhea (ie, Fitz–Hugh–Curtis syndrome) Inflam: pancreatitis, ruptured pancreatic/biliary/ lymph duct; bowel obstrxn, serositis (SLE) Hypoalbuminemic states: nephrotic syndrome, protein-losing enteropathy

- Ascites fluid total protein (**AFTP**): useful when SAAG ≥1.1 to distinguish cirrhosis (AFTP <2.5 g/dL) from cardiac ascites (AFTP ≥2.5 g/dL). Low AFTP (<1 g/dL) assoc. w/ ↑ risk of SBP (see "Cirrhosis" for guidelines on SBP Ppx based on AFTP).
- **Cell count:** normal limit of PMNs in ascitic fluid up to 250 PMNs/mm^3. Bloody tap (typically from traumatic para) can skew cell count; subtract 1 PMN for every 250 RBCs to correct PMN count. Ascitic PMNs ≥250 suggest infection.
- Other tests: amylase (pancreatitis, gut perf.); bili (test in dark brown fluid, suggests bile leak or proximal intestinal perf); TG (chylous ascites); BNP (HF); cytology (peritoneal carcinomatosis, ~95% Se w/ 3 samples). SBP a/w ↓ glc & ↑ LDH. Ascites cx (prior to abx if possible, should have both aerobic & anerobic w/ 10 mL per bottle).

Treatment (see "Cirrhosis" for details)

- If 2° to portal HTN: ↓ **Na intake** (<2 g/d) + **diuretics**; if refractory → LVP (serial) or TIPS
- If non-portal HTN related: depends on underlying cause (TB, malignancy, etc.)

Bacterial peritonitis (*Gut* 2012;61:297; *Hepatology* 2021;74:1014)

Ascites PMN	⊕ Ascites Culture	⊖ Ascites Culture
≥250/ µL	**Spontaneous bacterial peritonitis (SBP):** gut bacterial translocation to ascites. In cirrhosis, ↓ ascites opsonins (esp. if ↓AFTP) ↑ risk of infxn. Infection usually monomicrobial: most common → *E. coli*, *Klebs*, *S. pneumo*; rarely *Staph* & *Pseudo*. Rx 3rd-gen ceph; carbapenem if critically ill. **2° bacterial peritonitis:** 2/2 intra-abd abscess, perf. Runyon's criteria: AFTP >1 g/dL, glc <50	**Culture-⊖ neutrocytic ascites (CNNA):** cell counts suggest infxn but cx ⊖. No recent abx, w/o other explan. for counts. Often do have SBP and should be treated with empiric regimen.

	mg/dL, LDH > ULN for serum. Cx polymicrobial. Rx 3rd-gen ceph. + MNZ; urgent abd imaging ± ex lap.	
<250/ µL	**Nonneutrocytic bacterascites (NNBA):** ⊕ cx w/o ↑ PMNs. Natural course may resolve w/o Rx. Start abx if symptomatic; if asymptomatic repeat para in 48 hrs. Cx w/ 1 org.: Misc. GPC, *E. coli*, *Klebs*, misc. GNR.	(Normal)
Peritoneal dialysis-associated: cloudy fluid, abd pain, fever, nausea Dx can be made with >50 PMNs. Culture most often GPC (50%) or GNR (15%). Rx: vanc + gent (IV load, then administer in PD)		

BILIARY TRACT DISEASE

CHOLELITHIASIS (GALLSTONES)

Epidemiology & pathogenesis (*J Hepatol* 2016;65:146; *Gastro* 2016;151:351)

- Affects ~10% of Western populations, 15–25% of people develop sx over 10–15 y
- Bile = bile salts, phospholipids, cholesterol; ↑ cholesterol saturation in bile + accelerated nucleation + gallbladder hypomotility → gallstones
- Risk factors: ♀; South, Central, Native American; ↑ age (>40 y); obesity, TPN, rapid ↓ wt; dyslipidemia; preg., drugs (OCPs, estrogen, clofibrate, octreotide, ? GLP-1RA); ileal dis.
- Statin use ↓ risk of sx gallstones & cholecystectomy (*Hepatol Res* 2015;45:942)

Types of gallstones (*J Hepatol* 2016;65:146)

- Cholesterol (90%): 2 subtypes
  - mixed: contain >50% cholesterol; typically smaller, multiple stones
  - pure: 100% cholesterol; larger, yellow, white appearance
- Pigment (10%)
  - *Black:* unconjugated bili & calcium; seen w/ chronic hemolysis, cirrhosis, CF, Gilbert synd
  - *Brown:* stasis & infxn in bile ducts → bacteria deconjugate bilirubin → precipitates w/ Ca; found pred in bile ducts; seen w/ biliary strictures, parasites, post-cholecystectomy

Clinical manifestations

- Asx in ~80%. Biliary pain develops in 1–4%/y. Once sx, rate of complications ~1–3%/y.
- **Biliary pain** = **episodic RUQ or epigastric pain;** begins abruptly, continuous, resolves slowly, and lasts 30 min–3 h; ± radiation to scapula; precip by **fatty foods**; **nausea**
- Physical exam: afebrile, ± RUQ tenderness or epigastric pain

Diagnostic studies

- Labs normal in most
- RUQ U/S: Se & Sp >95% for stones >5 mm; should be performed after ≥8 h fast for distended, bile-filled gallbladder
- Endoscopic U/S (EUS): Se 94–98% in Pts w/ biliary pain but nl U/S (*J Hepatol* 2016;65:146)
- CT scan/KUB is less Se; stones often isodense w/o enough calcium & will be missed

Treatment (*Am Fam Physician* 2014;89:795; *J Hepatol* 2016;65:146)

- Cholecystectomy (CCY), usually laparoscopic, if symptomatic (sooner is better)
- CCY in *asx* Pts if: porcelain GB (wall calcification, ↑ risk of cancer), GB polyps >10 mm, stones >3 cm; undergoing bariatric surg., cardiac txp cand., hemolytic anemia (sickle cell)
- Options if ↑ risk for surgery: percutaneous drainage, endoscopic transpapillary drainage
- UDCA can be trialed for cholesterol stones w/ biliary pain or if poor surgical candidate, but takes ~3 mo to work; ↓ risk of gallstone formation that occurs w/ rapid wt ↓
- Pain: NSAIDs drugs of choice, efficacy ≈ opiates & avoids ↑ sphincter of Oddi pressure

Complications

- Cholecystitis: 20% of Pts with symptomatic biliary pain progress to cholecystitis w/in 2 y
- Choledocholithiasis → cholangitis or gallstone pancreatitis
- Mirizzi syndrome: hepatic duct compression by GB stone → jaundice, biliary obstruction
- Cholecystoenteric fistula: stone erodes through gallbladder into bowel, ~15% w/ colon
- Gallstone ileus: SBO (usually at term. ileum) due to stone in intestine that passed thru fistula
- Gallbladder carcinoma: ~1% in U.S., often found late stage, a/w poor prognosis

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Cholecystitis (*JAMA* 2022;327:965)

Pathogenesis

- Acute cholecystitis: stone impaction in cystic duct → inflammation behind obstruction → GB swelling ± secondary infection (50%) of biliary fluid
- Acalculous cholecystitis: GB stasis & ischemia (w/o cholelithiasis) → necroinflammation. Occurs in critically ill. A/w post-op major surgery, TPN, sepsis, trauma, burns, opiates, immunosuppression, infxn (eg, CMV, *Candida*, *Crypto, Campylobacter*, typhoid fever).

Clinical manifestations

- History: RUQ/epigastric pain ± radiation to R shoulder/back, nausea, vomiting, fever
- Physical exam: **RUQ tenderness**, **Murphy sign** = ↑ RUQ pain and inspiratory arrest with deep breath during palpation of R subcostal region, ± palpable gallbladder
- Laboratory evaluation: *may* see ↑ WBC, ↑ CRP, ± mild ↑ bilirubin, Aϕ, ALT/AST, amylase; if AST/ALT >500 U/L, bili >4 mg/dL or amylase >1000 U/L → choledocholithiasis

Diagnostic studies

- **RUQ U/S:** high Se & Sp for stones; *specific signs of cholecystitis:* GB wall thickening >4 mm, pericholecystic fluid, and a sonographic Murphy sign
- CT or MRI 2nd line if U/S inconclusive or if suspect complic. (emphysematous cholecystitis)
- **HIDA scan:** most Se test (80–90%) for acute cholecystitis. IV inj of HIDA (selectively secreted into bile). ⊕ if HIDA enters BD but not GB. 10–20% false ⊕ (cystic duct obstructed 2/2 chronic cholecystitis, lengthy fasting, liver disease).

Treatment (*NEJM* 2015;373:357; *J Clin Med* 2024;13:2695)

- NPO, IV fluids, nasogastric tube if intractable vomiting, analgesia
- **Antibiotics** (*E. coli*, *Klebsiella*, and *Enterobacter* sp. are usual pathogens)
- [2nd- or 3rd-generation cephalosporin or FQ] + MNZ or piperacillin-tazobactam
- **CCY** (typically laparoscopic) w/in 72 h from sx onset preferred to 7–10 days
- If initially unstable for surgery, EUS-guided transmural, ERCP-guided transcystic duct drainage, or perc. cholecystostomy (if w/o ascites or coagulopathy) are alternatives
- Intraoperative cholangiogram or ERCP to r/o choledocholithiasis in Pts w/ jaundice, cholangitis, or stone in BD on U/S (vide infra)

Complications

- Gangrenous cholecystitis: necrosis w/ risk of empyema and perforation
- Emphysematous cholecystitis: infection by gas-forming organisms (air in GB wall)
- Perforation: ~10% of cases, due to delay in diagnosis; pericholecystic abscess forms
- Post-CCY: bile duct leak, BD injury or retained stones, cystic duct remnant, sphincter of Oddi dysfxn

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Choledocholithiasis

Definition

- Gallstone lodged in common bile duct (CBD)

Epidemiology

- Occurs in 15% of Pts w/ gallbladder stones; can form de novo in CBD due to biliary stasis

Clinical manifestations

- RUQ/epigastric pain 2° obstrxn of bile flow → ↑ CBD pressure, jaundice, pruritus, nausea
- Rarely asymptomatic

Diagnostic studies (*J Hepatol* 2016;65:146; *Gastrointest Endosc* 2019;89:1075)

- Labs: ↑ bilirubin, Aϕ; transient spike in ALT or amylase suggests passage of stone
- RUQ U/S: BD stones seen ~50–80% of cases; usually inferred from dilated CBD (>6 mm)
- ERCP preferred modality when likelihood high (eg, visualized stone, cholangitis, bili >4, *or* dilated CBD on U/S + bili 1.8–4 mg/dL); cholangiogram (perc., operative) if ERCP unavailable or unsuccessful; EUS/MRCP to exclude BD stones if suspicion intermediate (eg, no stone, dilated ducts on U/S, bili 1.8–4 mg/dL, gallstone panc., age >55, or abnl non-bili LFT); MRCP often done first even when likelihood high

Treatment

- ERCP & papillotomy w/ stone extraction (± lithotripsy)
- CCY w/in 6 wk unless contraindicated (>15% Pts develop indication for CCY if unRx'd)

Complications

- Cholangitis, cholecystitis, pancreatitis, stricture

Cholangitis

Definition & etiologies (*World J Gasrointest Pathophysiol* 2018;9:1)

- Bile duct obstruction causes stasis → infection proximal to the obstruction
- Etiologies: **BD stone** (~85%); malignant (biliary, pancreatic) or benign stricture; infection w/ fluke (*Clonorchis sinensis, Opisthorchis viverrini*); recurrent pyrogenic cholangitis

Clinical manifestations

- Charcot triad: RUQ pain, jaundice, fever/chills; present in ~70% of Pts
- Reynolds pentad: Charcot triad + shock and Δ MS; present in ~15% of Pts

Diagnostic studies

- RUQ U/S: often demonstrates dilatation of bile ducts
- Labs: ↑ WBC (with left shift), bilirubin, Aϕ, amylase; may see ⊕ BCx
- ERCP; percutaneous transhepatic cholangiogram if ERCP unsuccessful

Treatment

- **Antibiotics** (broad spectrum) to cover common bile pathogens (vide supra); pip/tazo or combo regimen (ceftriaxone or ciprofloxacin + MNZ). If severe, carbapenems or pip/tazo.
- ~80% respond to conservative Rx and abx → biliary drainage on elective basis
- ~20% require **urgent biliary decompression** via ERCP (papillotomy, stone extraction, and/or stent insertion). If sphincterotomy cannot be performed (larger stones), decompression by biliary stent or nasobiliary catheter can be done; otherwise, percutaneous transhepatic biliary drainage or surgery.

ACID–BASE DISTURBANCES

General

Definitions

- **Acidemia** → pH <7.36, **alkalemia** → pH >7.44; pH = 6.10 + log([HCO_3]/[0.03×PCO_2])
- **Acidosis** → process that ↑ [H^+] or ↓ pH by ↓ HCO_3 or ↑ P_aCO_2
- **Alkalosis** → process that ↓ [H^+] or ↑ pH by ↑ HCO_3 or ↓ P_aCO_2
- Primary disorders: metabolic acidosis or alkalosis, respiratory acidosis or alkalosis
- Compensation
  - Respiratory: hyper/hypoventilation alters P_aCO_2 to counteract 1° metabolic process
  - Renal: excretion/retention of H^+/HCO_3^- to counteract 1° respiratory process
  - Respiratory compensation occurs in mins–hrs; renal compensation takes days
  - *Compensation usually never fully corrects pH*; if pH normal, consider mixed disorder

Consequences of Severe Acid–Base Disturbances (*NEJM* 1998;338:26 & 107)		
Organ System	**Acidemia (pH <7.20)**	**Alkalemia (pH >7.60)**
Cardiovascular	↓ contractility, arteriolar vasodilation ↓ MAP & CO; ↓ response to catecholamines ↑ risk of arrhythmias	Arteriolar vasoconstriction ↓ coronary blood flow ↑ risk of arrhythmias
Respiratory	Hyperventilation, ↓ resp. muscle strength	Hypoventilation
Metabolic	↑ K (resp. > metab.), insulin resistance	↓ K, Ca, Mg, PO_4
Neurologic	Δ MS	Δ MS, seizures, tetany

Workup (*NEJM* 2014;371:1434)

- **Traditional or physiologic approach** (Brønsted–Lowry definition of acids & bases)
  - Determine **primary disorder:** ✓ pH, P_aCO_2, HCO_3
  - Determine if **degree of compensation** is appropriate
  - Calculate the **anion gap**: Na − Cl − HCO_3

Primary Disorders				
Primary Disorder	**Problem**	**pH**	**HCO_3**	**P_aCO_2**
Metabolic acidosis	Gain of H^+ or loss of HCO_3	↓	⇓	↓
Metabolic alkalosis	Gain of HCO_3 or loss of H^+	↑	⇑	↑
Respiratory acidosis	Hypoventilation	↓	↑	⇑
Respiratory alkalosis	Hyperventilation	↑	↓	⇓

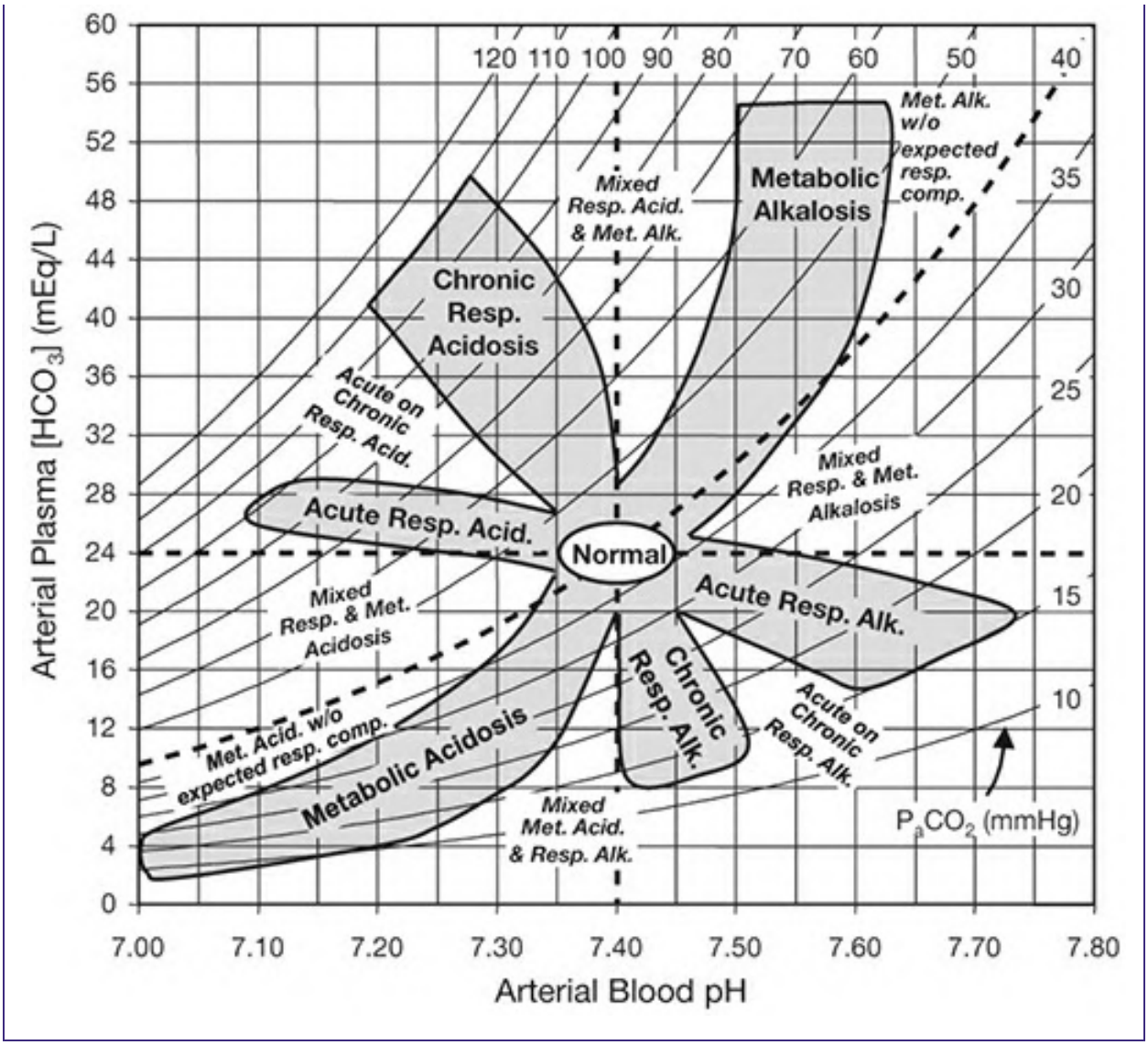
Compensation for Acid–Base Disorders (*NEJM* 2014;371:1434)	
Primary Disorder	**Expected Compensation**

Metabolic acidosis	↓ $P_aCO_2 = 1.2 \times \Delta HCO_3$ or $P_aCO_2 = (1.5 \times HCO_3) + 8 \pm 2$ (Winters' formula) (also, $P_aCO_2 \approx$ last 2 digits of pH)
Metabolic alkalosis	↑ $P_aCO_2 = 0.7 \times \Delta HCO_3$ or $P_aCO_2 = 0.7\ (HCO_3 - 24) + 40 \pm 2$ or $HCO_3 + 15$
Acute respiratory acidosis	↑ $HCO_3 = 0.1 \times \Delta P_aCO_2$ (also, ↓ pH = $0.008 \times \Delta P_aCO_2$)
Chronic respiratory acidosis	↑ $HCO_3 = 0.35 \times \Delta P_aCO_2$ (also, ↓ pH = $0.003 \times \Delta P_aCO_2$)
Acute respiratory alkalosis	↓ $HCO_3 = 0.2 \times \Delta P_aCO_2$ (also, ↑ pH = $0.008 \times \Delta P_aCO_2$)
Chronic respiratory alkalosis	↓ $HCO_3 = 0.4 \times \Delta P_aCO_2$

Mixed disorders (more than one primary disorder at the same time)

- If compensation less or greater than predicted, may be two disorders:
  P_aCO_2 too low → concomitant 1° resp. alk.; P_aCO_2 too high → concomitant 1° resp. acid.
  HCO_3 too low → concomitant 1° met. acid.; HCO_3 too high → concomitant 1° met. alk.
- Normal pH, *but…*
  ↑ P_aCO_2 + ↑ HCO_3 → resp. acid. + met. alk.
  ↓ P_aCO_2 + ↓ HCO_3 → resp. alk. + met. acid.
  Normal P_aCO_2 & HCO_3, *but* ↑ AG → AG met. acid. + met. alk.
  Normal P_aCO_2, HCO_3, & AG → no disturbance *or* non-AG met. acid. + met. alk.
- *Cannot* have resp. acid. (hypoventilation) and resp. alk. (hyperventilation) simultaneously

Figure 4-1 Acid–base nomogram



(Adapted from *Brenner & Rector's The Kidney*, 8th ed, 2007; *Practical Guide to the Care of the Medical Patient*, 7th ed, 2007)

- **ABG vs. VBG:** concordant for pH (~0.04), HCO_3 (~2 mEq) but **not** PCO_2 (~8±17 mmHg)
  VBG can be used to *screen* for hypercarbia w/ PCO_2 cutoff ≥45 mmHg (100% Se), **but** may not accurately assess *degree* of hypercarbia (*Am J Emerg Med* 2012;30:896)

Metabolic Acidosis

Initial workup (*NEJM* 2014;371:1434)

- ✓ **anion gap** (AG) = $Na^+ - (Cl^- + HCO_3^-)$ = unmeasured anions − unmeasured cations
  If ↑ glc, use measured *not* corrected Na
  Expected AG is [albumin] × 2.5 (ie, 10 if albumin is 4 g/dL, 7.5 if albumin is 3 g/dL)
  ↑ AG → ↑ unmeasured anions such as organic acids, phosphates, sulfates
  ↓ AG → ↓ alb or ↑ unmeasured cations (Ca, Mg, K, Li, Ig), bromide/iodine toxicity
- If ↑ AG, ✓ **delta–delta** ($\Delta/\Delta = \Delta AG/\Delta HCO_3$) to assess if there is an additional metabolic acid–base disturbance; ΔAG = (calculated AG − expected AG), $\Delta HCO_3 = (24 - HCO_3)$
  Δ/Δ = 1–2 → pure AG metabolic acidosis

Δ/Δ <1 → AG metabolic acidosis *and* simultaneous non-AG acidosis
Δ/Δ >2 → AG metabolic acidosis *and* simultaneous metabolic alkalosis
For pure lactic acidosis Δ/Δ 1.6 b/c of slow lactate clearance

Etiologies of AG Metabolic Acidosis	
Ketoacidosis	**Diabetes,** alcoholism (AKA), starvation, SGLT2i (*NEJM* 2015;372:546)
Lactic acidosis (*NEJM* 2014;371:2309)	**Type A:** hypoxic (eg, shock, mesenteric ischemia, CO poisoning, cyanide) **Type B:** nonhypoxic. ↓ clearance (eg, hepatic dysfxn) or ↑ generation [eg, malig ("Warburg effect," esp in high tumor burden), EtOH, thiamine def., meds (metformin, NRTIs, salicylates, propylene glycol, propofol, isoniazid, linezolid)] **D-lactic acidosis:** short bowel syndrome → precip by glc ingest → metab by colonic bacteria to D-lactate; not detected by standard lactate assay
Renal failure	Accumulation of organic anions (eg, phosphates, sulfates, etc.)
Ingestions (*NEJM* 2020;382:2544)	**Glycols:** *Ethylene* (antifreeze) → metab to glycolic and oxalic acids *Propylene* (pharmaceutical solvent, eg, IV diazepam, lorazepam, and phenobarbital; antifreeze) → lactic acidosis *Diethylene* (brake fluid) → diglycolic acid **5-oxoproline** (pyroglutamic acid): acetaminophen and penicillins → ↑ organic acid 5-oxoproline in susceptible Pts (malnourished, female, pregnant, renal failure, liver failure) **Methanol** (windshield fluid, antifreeze, solvents, fuel): metab to formic acid **Aspirin**: early resp alkalosis (CNS stim) + late metab acidosis (impairs oxidative phosphorylation → inorganic acids [eg, ketones, lactate])

"GOLD MARK" = Glycols, Oxoproline, Lactic, D-Lactic, Methanol, ASA, Renal, Ketoacidosis

Workup for AG metabolic acidosis (*AJKD* 2021;78:A16)

- ✓ for **ketonuria** (dipstick acetoacetate) or plasma β-hydroxybutyrate (βOHB)
  nb, urine acetoacetate often not present in early ketoacidosis due to shunting to βOHB; ∴ acetoacetate may later turn ⊕ but does not signify worsening disease
- If ⊖ ketones, ✓ **renal function, lactate, toxin screen, and osmolal gap**
- If obtunded or ↑↑ AG, check **osmolal gap** (OG) = measured osmoles − calculated osmoles
  Calculated osmoles = (2 × Na) + (glucose/18) + (BUN/2.8)
  (+ [EtOH/4.6] if ↑ EtOH level and want to test if other ingestions)
  OG >10 → suggests ingestion (vide infra) but lacks specificity (can be elevated in lactic acidosis, DKA, and alcoholic ketoacidosis due to acetone)
  High-dose lorazepam (>10 mg/h) a/w propylene glycol intoxication
  OG & AG vary based on timing, initially OG ↑, then ↓ w/ metabolism as AG ↑

Ingestions (*NEJM* 2018;378:270) Call poison control for guidance (800-222-1222)			
AG	**OG**	**Ingestion**	**Other Manifestations**
↑	nl	Acetaminophen	Hepatitis
		Salicylates	Fever, tachycardia, tinnitus; met. acid. + resp. alkalosis
↑	↑	Methanol	Δ MS, blurred vision, pupillary dilation, papilledema
↑	↑	Ethylene glycol	Δ MS, cardiopulm. failure, hypoCa. **Ca oxalate crystals** → AKI. Urine fluoresces under UV light.
nl/↑	↑	Propylene glycol	AKI, liver injury
↑	nl/↑	Diethylene glycol	AKI, N/V, pancreatitis, neuropathy, lactic acidosis

nl/↑	Isopropyl alcohol	Δ MS, fruity breath (acetone), pancreatitis, lactic acidosis
	Ethanol	Alcoholic fetor, Δ MS, hepatitis; keto + lactic acidosis ± met. alk. (vomiting)

Etiologies of Non-AG Metabolic Acidosis	
GI losses of HCO_3	Diarrhea, intestinal or pancreatic fistulas or drainage
RTAs	*See "Renal Tubular Acidoses"*
Early renal failure	Impaired generation of ammonia
Ingestions	Acetazolamide, sevelamer, cholestyramine, toluene
Dilutional	Due to rapid infusion of bicarbonate-free IV fluids
Posthypocapnia	Respiratory alkalosis → renal wasting of HCO_3; rapid correction of resp. alk. → transient acidosis until HCO_3 regenerated
Ureteral diversion	Colonic Cl^-/HCO_3^- exchange, ammonium reabsorption

Workup for non-AG metabolic acidosis

- Evaluate history for causes (vide supra)
- ✓ **urine anion gap** (UAG) = $(U_{Na} + U_K) - U_{Cl}$ = unmeasured anions (UA) − unmeasured cations (UC); NH_4^+ is primary UC. UAG is indirect assay for renal H^+ excretion.
- ⊖ UAG → ↑ renal NH_4^+ excretion → appropriate renal response to acidemia
  Ddx: GI causes (diarrhea, fistulas, ureteral diversion), IV NS, ingestions
- ⊕ UAG → failure of kidneys to generate NH_4^+
  Ddx: distal (type 1, usually ↓ K) or hypoaldo (type IV, usually ↑ K) RTA, early renal failure
- UAG unreliable in AKI/CKD, polyuria, Na depletion (U_{Na} <20), U_{pH} >6.5 & HAGMA (causes ⊕ UAG b/c excretion of organic anions) and less useful in prox RTA as variable. Then use U_{Osm} gap = measured U_{Osm} − [2×($Na^+ + K^+$) + BUN + glc (mmol/L)]. U_{Osm} gap <40 mmol/L indicates impaired NH_4^+ excretion.

Renal tubular acidoses (RTAs) (*Adv Ther* 2021;38:949)

- **Proximal** (Type II): ↓ proximal reabsorption of HCO_3
  1° (Fanconi's syndrome) = ↓ proximal reabsorption of HCO_3, PO_4, glc, amino acids
  Acquired: paraprotein (MM, amyloidosis), inflammatory disorders (Sjögren syndrome), cystinosis, metals (Pb, Cd, Hg, Cu), ↓ vit. D, PNH, renal Tx
  Meds: acetazolamide, aminoglycosides, ifosfamide, cisplatin, topiramate, tenofovir
- **Distal** (Type I): defective distal H^+ secretion
  1°, autoimmune (Sjögren's, RA, SLE), hypercalciuria, toluene inhalation, meds (ampho, Li, ifosfamide); normally a/w ↓ K; if with ↑ K → sickle cell, obstruction, renal transplant
- **Hypoaldo** (Type IV): hypoaldo → ↑ K → ↓ NH_3 synthesis → ↓ urine acid-carrying capacity
  ↓ renin: diabetic nephropathy, NSAIDs, chronic interstitial nephritis, calcineurin inhib, HIV
  ↓ aldo production: 1° AI, ACEI/ARBs, heparin, severe illness, inherited (↓ 21-hydroxylase)
  ↓ response to aldosterone
  Meds: K-sparing diuretics, TMP–SMX, pentamidine, calcineurin inhibitors
  Tubulointerstitial disease: sickle cell, SLE, amyloid, DM
- Combined (Type III): rarely discussed or clinically relevant, also called juvenile RTA, has distal &

proximal features, can be due to carbonic anhydrase II deficiency

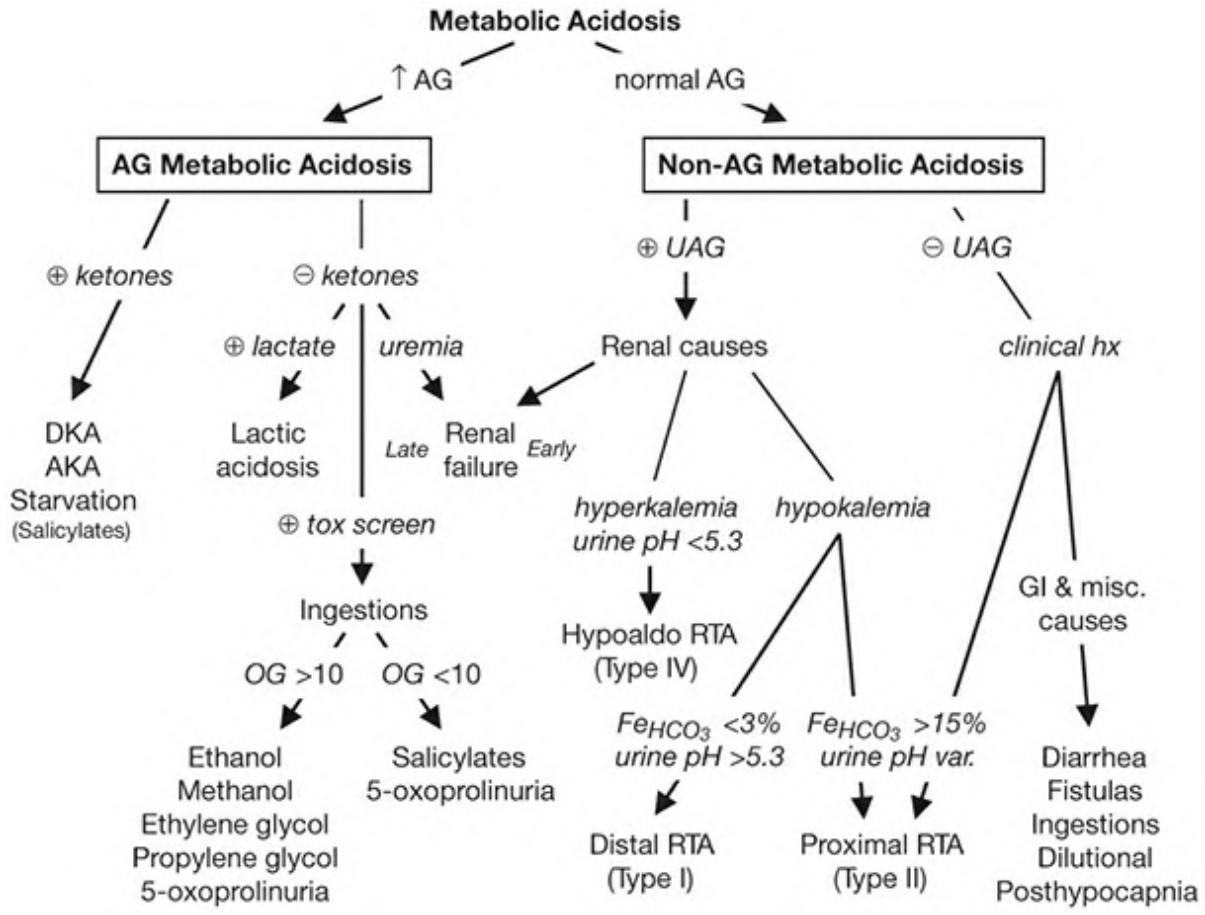
Renal Tubular Acidosis								
Location	**Type**	**Acidosis**	**UAG**	**HCO_3^-**	**U_{pH}**	**FE_{HCO3}[b]**	**K**	**Complications**
Proximal	II	Moderate	±	12–20	<5.3[a]	>15%	↓	Osteomalacia
Distal	I	Severe	⊕	<10	>5.3	<3%	↓[c]	Kidney stones
Hypoaldo	IV	Mild	⊕	>17	<5.3	<3%	↑	Hyperkalemia

[a]Urine pH will rise above 5.3 in the setting of HCO_3 load

[b]Fe_{HCO3} should be checked after an HCO_3 load

[c]See above for causes of distal RTA (Type I) associated with hyperkalemia

Figure 4-2 Approach to metabolic acidosis



Treatment of severe metabolic acidoses (pH <7.2) (*Nat Rev Nephrol* 2012;8:589)

- DKA: insulin, IVF, K repletion (*NEJM* 2015;372:546); AKA: dextrose, IVF, replete K, Mg, PO_4
- Lactic acidosis: treat underlying condition, avoid vasoconstrictors, avoid "Type B" meds
- Renal failure: hemodialysis
- Methanol & ethylene glycol: fomepizole (20 mg/dL), vit. B_1 & B_6 (ethylene glycol), folate (methanol), dialysis (if AKI, VS unstable, vision Δ or >50 mg/dL) (*NEJM* 2018;378:270)

- Alkali therapy: if pH <7.1 or <7.2 and coexisting AKI (may ↓ mortality; *Lancet* 2018;392:31)
- $NaHCO_3$: amps by IV push or infusion of three 50-mmol amps in 1 L D_5W if less urgent
  Can estimate mmol of HCO_3 needed as [desired − current $HCO_3]_{serum}$ × wt (kg) × 0.4
  Side effects: ↑ volume, ↑ Na, ↓ ICa, ↑ P_aCO_2 (& ∴ intracellular acidosis; ∴ *must ensure adequate ventilation* to blow off CO_2)

Metabolic Alkalosis

Pathophysiology (*CJASN* 2020;15:1848)

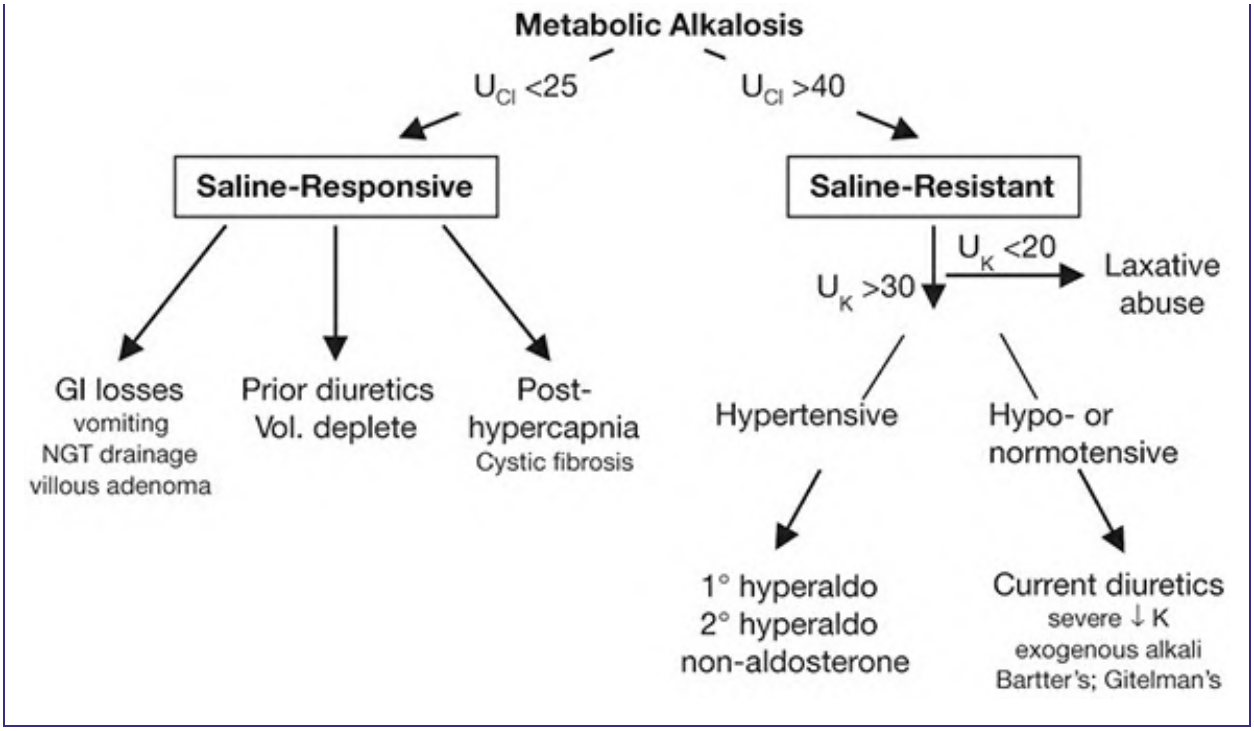
- Saline-responsive etiologies require *initiating event* and *maintenance phase*
- *Initiating event:* net HCO_3^- reabsorption (due to loss of volume, Cl^-, and/or K^+) or loss of H^+
  Loss of H^+ (± Cl^-) from GI tract, kidneys, or transcellular shift in hypokalemia
  Contraction alkalosis: loss of HCO_3^--poor fluid → extracellular fluid "contracts" around fixed amount of HCO_3^- → ↑ HCO_3^- concentration
  Exogenous alkali: iatrogenic HCO_3^- (with renal impairment), milk-alkali syndrome
  Posthypercapnia: resp. acidosis → compensation with H^+ excretion and HCO_3^- retention; rapid correction of hypercapnia (eg, intubation) → transient excess HCO_3^-
- *Maintenance phase*
  Volume depletion → ↑ ATII → ↑ PCT reabsorption of HCO_3^- & ↑ aldosterone (vide infra)
  Cl^- depletion → ↓ Cl^- uptake in macula densa → ↑ RAS & ↑ CCD Cl^-/HCO_3^- exchanger
  Hypokalemia → transcellular K^+/H^+ exchange; intracellular acidosis → HCO_3^- reabsorption and ammoniagenesis & ↑ distal H^+-K^+-ATPase activity → HCO_3^- retention
  Hyperaldosteronism (1° or 2°) → ↑ CCD α-intercalated H^+ secretion w/ HCO_3^- retention & Na^+ reabsorption in principal cell → H^+ secretion (for electrical neutrality)

Etiologies of Metabolic Alkalosis	
Saline responsive U_{Cl} <25	**GI loss of H^+**: emesis, NGT suction, villous adenoma, chloridorrhea **Renal loss**: loop/thiazide, ↓ Cl intake, milk-alkali, Pendred syndrome Posthypercapnia, sweat losses in cystic fibrosis
Saline resistant U_{Cl} >40	*Hypertensive* **(mineralocorticoid excess)** 1° hyperaldosteronism (eg, Conn's) 2° hyperaldosteronism (eg, renovascular dis., renin-secreting tumor) Non-aldo (Cushing's, Liddle's, exog. mineralocorticoids, licorice) *Normotensive* Severe hypokalemia (K <2); exogenous alkali load (w/ AKI or ↓ vol) Bartter's syndrome (loop-like); Gitelman's syndrome (thiazide-like)

Workup

- Check **volume status** and **U_{Cl}**
  U_{Cl} <25 mEq/L → saline responsive
  U_{Cl} >40 mEq/L → saline resistant (unless currently receiving diuretics)
  (U_{Na} unreliable determinant of volume status in alkalemia → ↑ HCO_3^- excretion → ↑ Na excretion; negatively charged HCO_3^- w/ Na^+ maintaining electrical neutrality)
  If U_{Cl} >40 and volume replete, ✓ U_K; U_K <20 laxative abuse; U_K >30, ✓ **blood pressure**

Figure 4-3 Approach to metabolic alkalosis



Treatment of severe metabolic alkalosis (pH >7.6) (*Am J Kidney Dis* 2022;80:536)

- If saline responsive: resuscitate with Cl-rich solution (NS), replete K, d/c diuretics
  cardiopulmonary disease precludes hydration, can use KCl, acetazolamide, HCl
- Hyperaldosteronism: treat underlying condition, K-sparing diuretic, resect adenoma if 1°

Respiratory Acidosis (*Am J Kidney Dis* 2023;82:347)

Etiologies (also see "Hypercapnia"; $P_aCO_2 = VCO_2 / [RR \times (V_T - V_D)]$)

- ↑ **CO_2 production** (↑ VCO_2): fever, thyrotoxicosis, sepsis, steroids, overfeeding (carbs)
- **CNS depression** (↓ RR and/or V_T): sedatives (opiates, benzos, etc.), CNS trauma, central sleep apnea, obesity, hypoventilation, hypothyroidism
- **Neuromuscular disorders** (↓ V_T): Guillain–Barré, poliomyelitis, ALS, MS, paralytics, myasthenia gravis, muscular dystrophy, severe ↓ P & K, high spinal cord injury
- **Chest wall** (↓ V_T): PTX, hemothorax, flail chest, kyphoscoliosis, ankylosing spondylitis
- **Upper airway** (↓ V_T): foreign body, laryngospasm, OSA, esophageal intubation
- **Lower airway (gas exchange)** (↑ V_D and/or ↓ V_T): asthma, COPD, pulm edema, IPF
  Often hypoxia → ↑ RR → resp. alk., but muscle fatigue → resp. acid.
- Postinfusion of bicarbonate in acidemic Pt w/ limited ability to ↑ minute ventilation

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Respiratory Alkalosis

Etiologies (*Am J Kidney Dis* 2023;82:347)

- **Hypoxia → hyperventilation:** pneumonia, CHF, PE, restrictive lung disease, anemia
- **Primary hyperventilation**
  CNS stimulation, pain, anxiety, trauma, stroke, CNS infection, pontine tumors
  drugs: salicylate toxicity (early), β-agonists, progesterone, methylxanthines, nicotine
  pregnancy, sepsis, hepatic failure, hyperthyroidism, fever

- **Pseudorespiratory alkalosis:** ↓ perfusion w/ preserved ventilation (eg, CPR, severe HoTN) → ↓ delivery of CO_2 to lungs for excretion; low P_aCO_2 but ↑ tissue CO_2

SODIUM AND WATER HOMEOSTASIS

OVERVIEW

General (*NEJM* 2015;372:55 & 373:1350; *AJKD* 2020;75:272)

- Disorders of serum sodium are generally due to Δs in *total body water*, not sodium
- Hyper- or hypo-osmolality → rapid water shifts → Δs in brain cell volume → Δ MS, seizures

Key hormones

- **Antidiuretic hormone (ADH):** primary hormone that regulates *sodium concentration*
  Stimuli: hyperosmolality (290–295 mOsm), ↓↓ effective arterial volume, angiotensin II
  Action: insertion of aquaporin-2 channels in principal cells → passive water reabsorption
  urine osmolality is an indirect functional assay of the ADH-renal axis
  U_{Osm} range: 50 mOsm/L (no ADH) to 1200 mOsm/L (maximal ADH)
- **Aldosterone:** primary hormone that regulates *total body sodium* (and ∴ volume)
  Stimuli for secretion: hypovolemia (via renin and angiotensin II), hyperkalemia
  Action: iso-osmotic principal cell reabsorption of Na via epithelial Na channel (ENaC) in exchange for K^+ or H^+

HYPONATREMIA

Pathophysiology (*AJKD* 2020;75:272; *JAMA* 2022;323:280)

- **Excess H_2O relative to Na**, usually due to ↑ **ADH**
- ↑ ADH may be *appropriate* (eg, hypovolemia or hypervolemia with ↓ EAV)
- ↑ ADH may be *inappropriate* (SIADH)
- Rarely, ↓ ADH (appropriately suppressed), but kidneys unable to maintain nl $[Na]_{serum}$
  at steady state, solute intake = solute excretion; urine output = solute excretion/U_{Osm}
  nl dietary solute load ~750 mOsm/d, min U_{Osm} = 50 mOsm/L, ∴ UOP can be up to ~15 L
  ↑ *H_2O intake (1° polydipsia):* ingestion of massive quantities (usually >15 L/d) of free H_2O overwhelms diluting ability of kidney → H_2O retention
  ↓ solute intake ("tea & toast" & beer potomania): ↓↓ daily solute load → insufficient solute to excrete H_2O intake (eg, if only 250 mOsm/d, minimum U_{Osm} = 50 mOsm/L → excrete in ~5 L; if H_2O ingestion exceeds this amount → H_2O retention)

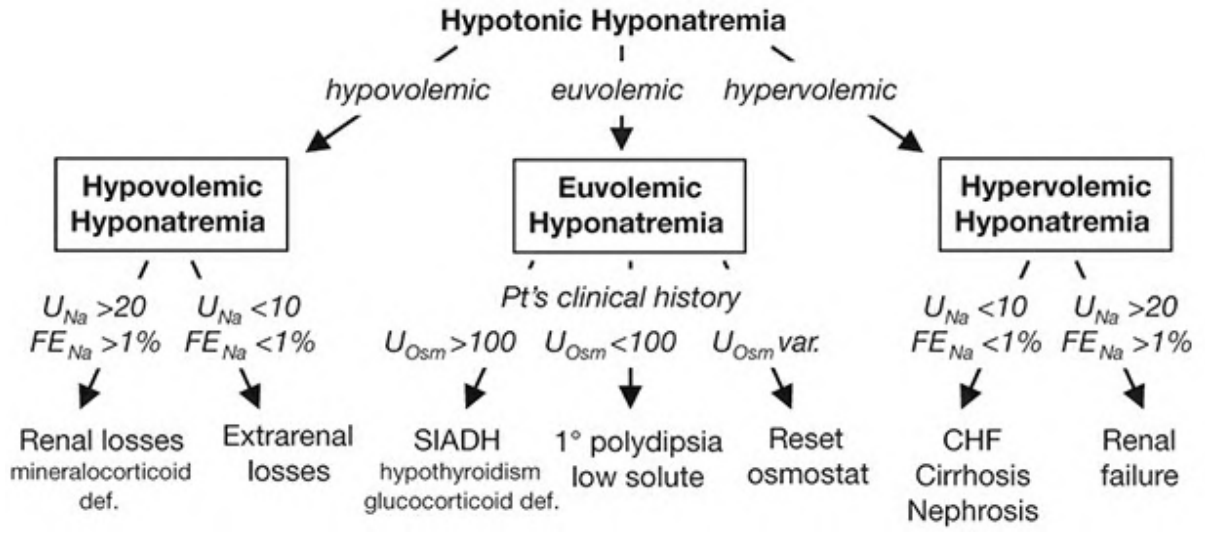
Workup (*AJKD* 2020;75:272; *JAMA* 2022;323:280)

- **History:** (1) acute vs. chronic (>48 h); (2) sx severity; (3) risk for neuro complications (alcoholism, malnourished, cirrhosis, older women on thiazides, hypoxia, hypoK)
- Measure **plasma osmolality**
  Hypotonic (P_{Osm} <280) most common scenario; true excess of free H_2O relative to Na
  Isotonic (P_{Osm} 280–295): rare lab artifact from hyperlipidemia or hyperproteinemia
  Hypertonic (P_{Osm} >295): excess of another effective osmole (eg, glucose, mannitol) that draws H_2O intravascularly; for each 100 mg/dL ↑ glc >100 mg/dL → ↓ [Na] by ~2 mEq/L. If

P_{Osm} elevated due to an *ineffective* osmole (eg, urea, ethanol), then plasma is *hypotonic* and should treat as such (*JAMA* 1999;159:333).

- For hypotonic hyponatremia, ✓ **volume status** (JVP, skin turgor, dry axilla, mucous membranes, edema, ascites), effusions, vital signs, orthostatics, BUN/Cr, $FE_{Uric\ Acid}$, U_{Na}
- Measure **U_{Osm}**, although useful for dx in limited circumstances, b/c almost always >300
  U_{Osm} <100 in ↑H_2O intake (1° polydipsia) or ↓ solute intake (beer potomania, "tea & toast")
  U_{Osm} >300 does not mean SIADH; must determine if ↑ ADH appropriate or inappropriate
  however, U_{Osm} can be important when deciding on *treatment* (vide infra)
- If euvolemic and ↑ U_{Osm}, evaluate for glucocorticoid insufficiency and hypothyroidism
- If available, consider $FE_{Uric\ Acid}$ as >12% suggests SIADH (*J Clin Endo* 2008;93:2991)

Figure 4-4 Approach to hyponatremia



Hypovolemic hypotonic hyponatremia (ie, ↓↓ total body Na, ↓ TBW)

- **Renal losses** (U_{Na} >20 mEq/L, FE_{Na} >1%): diuretics (esp. thiazides, because loop diuretics ↓ tonicity of medullary interstitium, Δ for H_2O absorption, & ∴ urine concentrating ability), salt-wasting nephropathy, cerebral salt wasting, mineralocorticoid deficiency
- **Extrarenal losses** (U_{Na} <10 mEq/L, U_{Cl} <10 mEq/L if alkalemia, FE_{Na} <1%): hemorrhage, GI loss (diarrhea or vomiting), third-spacing (pancreatitis), ↓ PO intake, insensible losses

Euvolemic hypotonic hyponatremia (ie, ↑ TBW relative to total body Na)

- **SIADH** (euvolemia or mild hypervolemia, typically **inapprop U_{Osm} >100,** U_{Na} >20 mEq/L)
  Malignancy: lung (SCLC), brain, GI, GU, lymphoma, leukemia, thymoma, mesothelioma
  Pulmonary: pneumonia, TB, aspergillosis, asthma, COPD, PTX, mechanical ventilation
  Intracranial: trauma, stroke, SAH, seizure, infxn, hydrocephalus, Guillain–Barré
  Drugs: antipsychotics, antidepress. (SSRI, TCA, MAOi), haloperidol, chemo (vincristine, cisplatin), AVP, MDMA, NSAIDs, opiates, amiodarone (*AJKD* 2008;52:144)
  Miscellaneous: pain, nausea, postoperative state
- **Endocrinopathies:** ↑ ADH activity seen in *glucocorticoid deficiency* (cosecretion of ADH & CRH) and *severe hypothyroidism/myxedema coma* (↓ CO/SVR → ADH release & ↓ GFR)
- **Psychogenic polydipsia** (U_{Osm} <100, ↓ $FE_{Uric\ Acid}$): usually intake >15 L/d
- **Low solute** (↓ U_{Na}, ↓ U_{Osm}) "tea & toast"; beer potomania
- Reset osmostat: chronic malnutrition (↓ intracellular osmoles) or pregnancy (hormonal

effects) → ADH physiology reset to regulate a lower $[Na]_{serum}$

Hypervolemic hypotonic hyponatremia (ie, ↑ total body Na, ↑↑ TBW)

- ↓ EAV → ↑ RAAS → ↑ aldosterone & ↑ adrenergic tone → ↑↑ ADH (*Am J Med* 2013;126:S1)
- **CHF** (↓ CO & renal venous congestion → ↓ EAV; U_{Na} <10 mEq/L, FE_{Na} <1%)
- **Cirrhosis** (splanchnic arterial vasodilation + ascites → ↓ EAV; U_{Na} <10 mEq/L, FE_{Na} <1%)
- **Nephrotic syndrome** (hypoalbuminemia → edema → ↓ EAV; U_{Na} <10 mEq/L, FE_{Na} <1%)
- **Advanced renal failure** (diminished ability to excrete free H_2O; U_{Na} >20 mEq/L)

Treatment (*CJASN* 2018;13:641 & 984; *JAMA* 2022;323:280)

- **Approach:** depends on *volume status*, *acuity* of hyponatremia, and if *symptomatic*
  Acute sx: *initial* rapid correction of $[Na]_{serum}$ (2 mEq/L/h for the first 2–3 h) until sx resolve
  Asx or chronic symptomatic: correct $[Na]_{serum}$ at rate of ≤0.5 mEq/L/h
  Rate ↑ Na *should not exceed 6* (chronic) to *8* (acute) mEq/L/d to avoid central pontine myelinolysis/osmotic demyelination (CPM/ODS: paraplegia, dysarthria, dysphagia)
  If severe (<120) or neuro sx: consider 3% NaCl. dDAVP 1–2 µg q8h in consultation with nephrology (to prevent rapid overcorrection) (*AJKD* 2013;61:571; *CJASN* 2018;13:641).
- **Frequent lab draws** and **IVF rate adjustments** are cornerstones of treatment
- **Rapid correction:** a/w CPM/ODS (esp if chronic and Na <120 mEq/L). Should be emergently reversed w/ dDAVP ± D_5W; partial neuro recovery possible (*CJASN* 2014;9:229). Rates of CPM/ODS low; correction rates >8 mEq/d not always a/w poor outcomes, though cautious correction generally preferred (*NEJM Evid* 2023;EVIDoa2200215 & 2300107).
- **Effect of IV fluids**: complex as depends not only on $[Na]_{infusate}$ but also UOP and U_{Osm}

Scenario	Formula to Estimate New $[Na]_{serum}$ after 1 L infusion
If minimal UOP and none of infused Na excreted	$\frac{(\text{current } [Na]_{serum} \times TBW) + [Na]_{infusate}}{TBW + 1}$
If euvolemic (eg, in SIADH) & all infused Na excreted	$\frac{(\text{current } [Na]_{serum} \times TBW) + [Na]_{infusate} - [Na]_{infusate}}{TBW + 1 - \frac{\text{infusate}_{Osm}}{U_{Osm}}}$

In SIADH "fixed" high U_{Osm}. ∴ in SIADH w/ U_{Osm} 616, 1 L NS (154 mEq Na or 308 mOsm solute in 1 L H_2O) will be excreted in 0.5 L H_2O → net *gain* 0.5 L H_2O.
∴ NS *worsens* $[Na]_{serum}$ if U_{Osm} > $infusate_{Osm}$. In contrast, 1 L 3% NaCl (1026 mOsm) would be excreted in ~1.7 L urine → net *loss* 0.7 L H_2O. ∴ 3% saline ↑ $[Na]_{serum}$.

Effect of 1 L infusion in 70-kg male w/ $[Na]_{serum}$ 110 mEq/L & U_{Osm} 616 mOsm/kg			
IVF Type	**$[Na]_{content}$**	**No UOP**	**Infused Na excreted**
0.9% NaCl	154 mEq/L	+1.0 mEq/L	−1.3 mEq/L
3% NaCl	513 mEq/L	+9.4 mEq/L	+1.8 mEq/L

- **Hypovolemic hyponatremia:** volume repletion with isotonic 0.9% saline at a **slow rate**. Once volume replete → stimulus for ADH removed (w/ very short ADH $t_{½}$) → kidneys excrete free H_2O → serum Na will correct rapidly (D_5W ± dDAVP if overcorrection)

- **SIADH** (*AJKD* 2020;76:203): **fluid restrict** + treat underlying cause
  - **hypertonic saline** (± loop diuretic; *AJKD* 2020;76:203) if sx or Na fails to ↑ w/ fluid restriction
    - Intermittent bolus of 3% saline (~2 mL/kg q6h) vs. continuous infusion (~0.5 mL/kg/h) similar (*JAMA IM* 2021;181:81) when moderate symptoms. Must recheck serum Na frequently during hypertonic use (at least q2h).
  - NaCl tabs if chronic and no CHF. Consider urea 0.25–0.5 g/kg/d (*CJASN* 2018;13:1627).
  - aquaresis: vaptans (vasopressin receptor antag) for refractory SIADH (*NEJM* 2015;372:23)
- **Hypervolemic hyponatremia:** free water restrict (1st line), diurese w/ loop diuretics (avoid thiazides) & ↑ EAV (vasodilators to ↑ CO in CHF, colloid infusion in cirrhosis)
  - vaptans sometimes used; however, no mortality benefit, hypoNa recurs after stopping drug, high risk of overcorrection, relatively contraindicated in cirrhosis (*NEJM* 2015;372:2207)

Hypernatremia

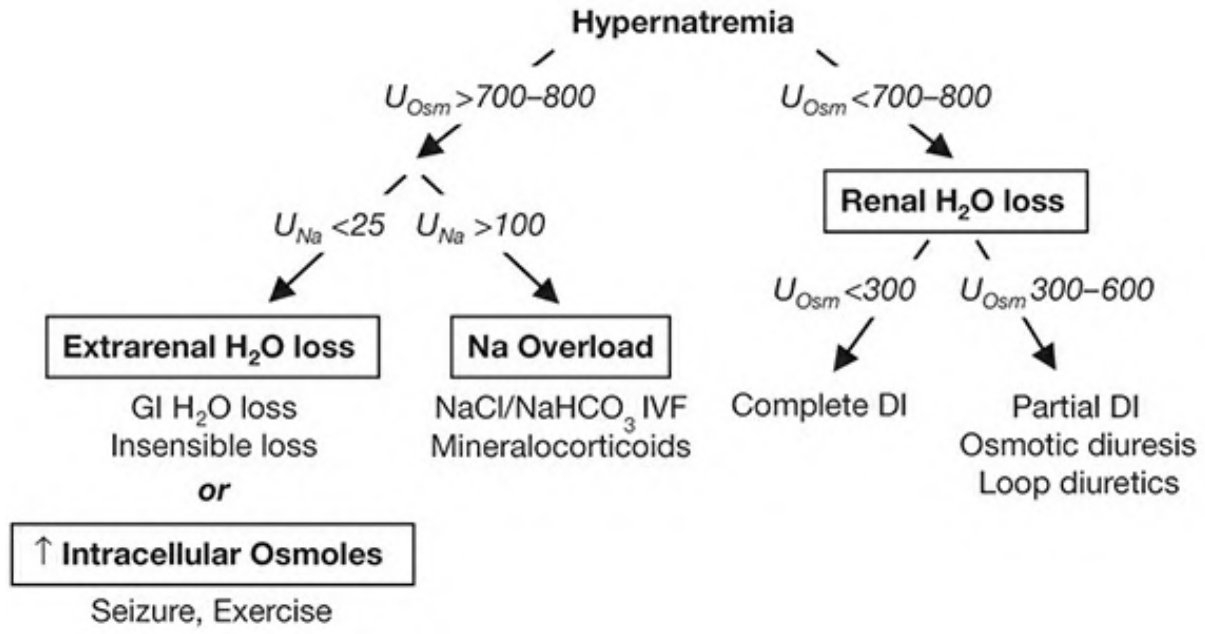
Pathophysiology (*AJKD* 2020;75:272)

- Deficit of water relative to sodium; by definition, all hypernatremic Pts are hypertonic
- Usually **loss of hypotonic fluid** (ie, "dehydration"); occasionally infusion of hypertonic fluid, post-ATN diuresis w/ loss of low or electrolyte-free water (*Am J Neph* 2012;36:97)
- ***And* impaired access to free water** (eg, intubation, Δ MS, elderly): hypernatremia is a powerful thirst stimulus, ∴ usually only develops in Pts w/o access to H_2O or ill

Workup

- ✓ U_{Osm}, U_{Na}, volume status (vital signs, orthostatics, JVP, skin turgor, BUN, Cr)

Figure 4-5 Approach to hypernatremia



Extrarenal H_2O loss (U_{Osm} >700–800)

- **GI H_2O loss:** vomiting, NGT drainage, osmotic diarrhea, fistula, lactulose, malabsorption
- **Insensible loss:** fever, exercise, ventilation, burns

Renal H_2O loss (U_{Osm} <700–800)

- **Diuresis:** osmotic (glucose, mannitol, urea), loop diuretics
- **Diabetes insipidus** (*Nat Rev Nephrol* 2015;11:576)
  ADH deficiency (central) or resistance (nephrogenic)
  Central: hypothalamic or posterior pituitary disease (congenital, trauma/surgery, infiltrative/IgG4); also idiopathic, hypoxic/ischemic encephalopathy (shock, Sheehan's syndrome), anorexia, sarcoidosis, histiocytosis, drugs: EtOH, phenytoin, snake venom, tumors: craniopharyngioma, germinoma, lymphoma, leukemia, meningioma, pituitary
  Nephrogenic (*Annals* 2006;144:186)
  congenital (ADH receptor V2 mutation, aquaporin-2 mutation)
  drugs: **lithium**, amphotericin, demeclocycline, foscarnet, cidofovir, ifosfamide
  metabolic: **hypercalcemia**, **severe hypokalemia**, protein malnutrition
  tubulointerstitial: **postobstruction**, **recovery phase of ATN**, PKD, sickle cell, Sjögren's, amyloid, pregnancy (placental vasopressinase)
  DI (thirst drive intact) usually presents as *severe* polyuria and *mild* hypernatremia

Other (U_{Osm} >700–800)

- **Na overload:** hypertonic saline (eg, resuscitation w/ $NaHCO_3$), mineralocorticoid excess
- **Seizures**, ↑ **exercise:** ↑ intracellular osmoles → H_2O shifts → transient ↑ $[Na]_{serum}$

Treatment (*AJKD* 2020;75:272)

- **Restore access to H_2O** or supply daily requirement of H_2O (≥1 L/d)
- **Replace free H_2O deficit** (also replace concurrent volume deficit if appropriate):

$$\text{Free } H_2O \text{ deficit (L)} = \frac{[Na]_{serum} - 140}{140} \times TBW$$

TBW = wt (kg) × 0.6 (♂) or 0.5 (♀)
if elderly use 0.5 (♂) or 0.45 (♀)

shortcut: for typical 70-kg man, free H_2O deficit (L) ~$([Na]_{serum} - 140)/3$

$$\Delta\,[Na]_{serum} \text{ per L infusate} = \frac{[Na]_{serum} - [Na]_{infusate}}{TBW + 1}$$

eg, 1 L D_5W given to 70-kg man w/ [Na] = 160 mEq/L will ↓ $[Na]_{serum}$ by 3.7 mEq
nb, do not forget to correct Na if hyperglycemia also present

- Rate of correction depends on acuity of onset and risk:
  chronic (>48 hr): ~12 mEq/d appears safe w/o risk of cerebral edema (*CJASN* 2019;14:656)
  acute (<48 hr): may ↓ Na by 2 mEq/L/h until Na 145
  hyperacute (min–hrs) & life threatening (ICH, seizure): rapidly infuse D_5W ± emergent HD
- *Estimate:* in 70-kg man, 125 mL/h of free H_2O will ↓ [Na] by ~0.5 mEq/L/h
- ½ NS (77 mEq/L) or ¼ NS (38 mEq/L) provides both volume & free H_2O (500 or 750 mL of free H_2O per L, respectively); can give free H_2O via NGT/OGT
- Formulas provide only estimates; ∴ recheck serum Na frequently
- **DI and osmotic diuresis:** see "Polyuria"
- **Na overload:** D_5W + diuretic. Consider HD if life threatening (ICH, hypertonia, seizures).

Polyuria

Definition and pathophysiology

- **Polyuria** defined as >3 L UOP per day
- Due to an *osmotic* or a *water diuresis*; almost always due to osmotic diuresis in inpatients

Workup

- Perform a timed urine collection (6 h sufficient) and measure U_{Osm}
- 24-h osmole excretion rate = 24-h UOP (actual or estimate) × U_{Osm}
  >1000 mOsm/d → osmotic diuresis; <800 mOsm/d → water diuresis

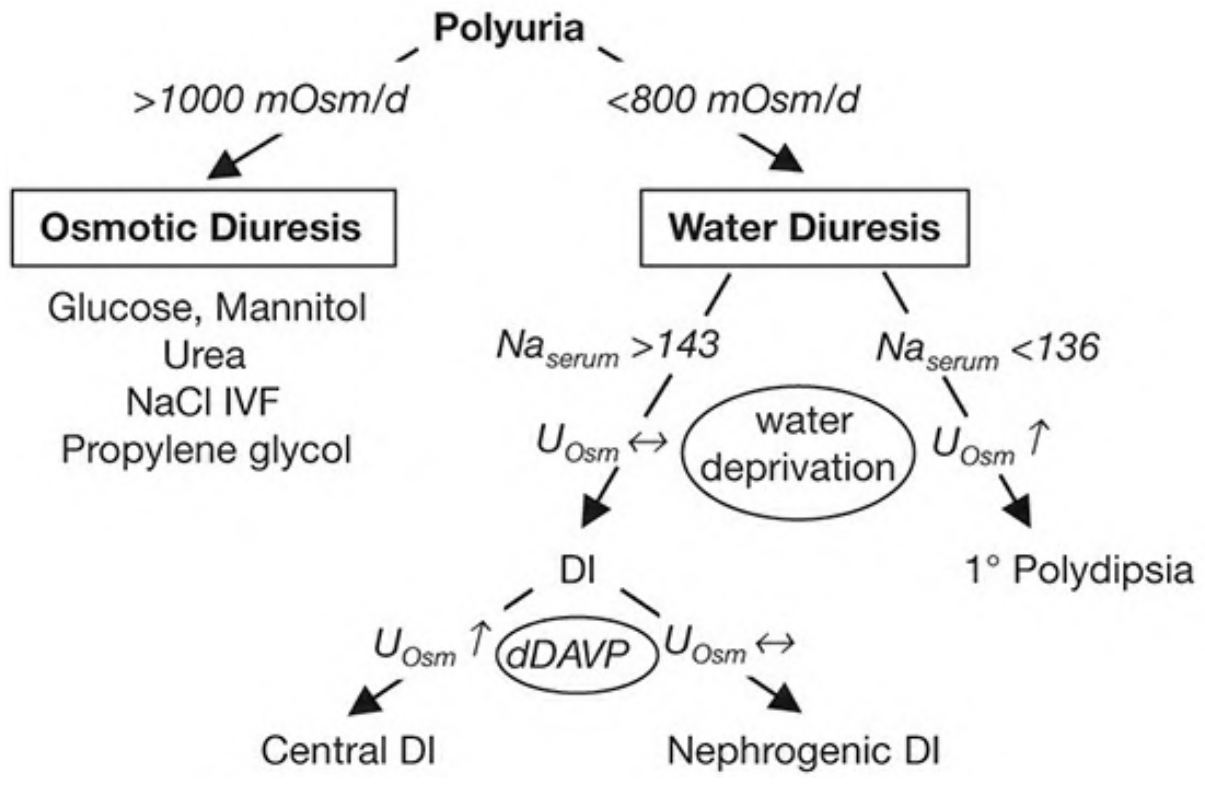
Osmotic diuresis

- Etiologies
  Hyperglycemia (>180 exceeds PCT reabsorption), mannitol, propylene glycol
  Na: NaCl IVF, recovering AKI (eg, postobstruction)
  Urea: ↑ protein feeds, hypercatabolism (burns, steroids), GI bleed, resolving azotemia

Water diuresis

- Etiologies: DI (Na_{serum} >143) or **1**° **polydipsia** (Na_{serum} <136)
  see “Hypernatremia” for list of causes of central and nephrogenic DI
- Workup of DI: U_{Osm} <300 (complete) or 300–600 (partial)
  water deprivation test (rarely used)
  hypertonic saline-stimulated plasma copeptin >4.9 pmoL/L indicates 1° polydipsia (97% accuracy vs. 77% for water deprivation; *NEJM* 2018;379:428)

Figure 4-6 Approach to polyuria



Treatment

- **1° polydipsia:** treat psychiatric illness, check meds, restrict access to free H_2O
- **Osmotic diuresis:** address underlying cause, replace free H_2O deficit (see "Hypernatremia" for formula to calculate) and ongoing losses
- **DI:**
  Central DI: desmopressin (dDAVP, 1st line), low Na/protein diet + HCTZ, chlorpropamide
  Nephrogenic DI: treat underlying cause if possible; Na restriction + HCTZ (mild volume depletion → ↓ delivery of filtrate for free H_2O absorption), consider amiloride for Li-induced DI (*Kid Int* 2009;76:44), indomethacin *(NEJM* 1991;324:850) or trial desmopressin
  Pregnancy-induced DI: due to vasopressinase from placenta, ∴ Rx w/ dDAVP

POTASSIUM HOMEOSTASIS

Overview (*NEJM* 2015;373:60)

- Renal: K excretion regulated at **distal nephron** (CCD) by principal & α-intercalated cells
  Distal Na delivery & urine flow: Na absorption → lumen electronegative → K secretion
  Metabolic alkalemia and aldosterone: increase Na absorption and K secretion
  nb, diurnal urinary K excretion (day > night), ∴ 24-h sample preferred over spot
- Transcellular shifts: most common cause of acute Δ in serum K (98% intracellular)
  Acid–base disturbance: K^+/H^+ exchange across cell membranes
  Insulin → stimulates Na-K ATPase → hypokalemia (mitigates postprandial ↑ K)
  Catecholamines → stimulate Na-K ATPase → hypokalemia; reversed by β-blockers
  Massive necrosis (eg, tumor lysis, rhabdo, ischemic bowel) → release of intracellular K
  Hypo- or hyperkalemic periodic paralysis: rare disorders due to channel mutations
- Diet: alone rarely causes ↑ or ↓ K (total body store ~3500 mEq, daily intake ~100 mEq)

HYPOKALEMIA (NEJM 2024;390:1514)

Transcellular shifts ($U_{K:Cr}$ <13 mEq/g)

- Alkalemia, insulin, catecholamines, β_2-agonists, hypothermia, hypokalemic/thyrotoxic periodic paralysis, acute ↑ hematopoiesis (megaloblastic anemia Rx w/ B_{12}, AML crisis), chloroquine; overdose: Ba/Cs, antipsychotics (risperidone, quetiapine), theophylline

GI potassium losses ($U_{K:Cr}$ <13 mEq/g)

- Lower GI losses *plus* metabolic acidosis: diarrhea, laxative abuse, villous adenoma
- Vomiting & NGT drainage usually manifest as *renal losses* due to 2° hyperaldo & met. alk.

Renal potassium losses ($U_{K:Cr}$ >13 mEq/g)

- Hypotensive or normotensive
  Acidosis: DKA, RTA (distal RTAs > proximal RTAs)
  Alkalosis: diuretics (thiazide > loop), vomiting/NGT drainage (via 2° hyperaldosteronism)
    Bartter's syndrome (loop of Henle dysfxn → furosemide-like effect; *JASN* 2017;28:2540)
    Gitelman's syndrome (DCT dysfxn → thiazide-like effect; *KI* 2017;91:24)
  Drugs: PCN, aminoglycosides, ampho, foscarnet, cisplatin, ifosfamide
  ↓ Mg: less Mg to inhibit principal cell ROMK channel, ∴ ↑ K secretion (*JASN* 2010;21:2109)
- Hypertensive: mineralocorticoid excess
  1° hyperaldosteronism (eg, Conn's syndrome, glucocorticoid-remediable aldosteronism)

2° hyperaldosteronism (eg, renovascular disease, renin-secreting tumor)
Non-aldo mineralocorticoid (eg, Cushing's, Liddle's, exogenous, licorice, antifungals)

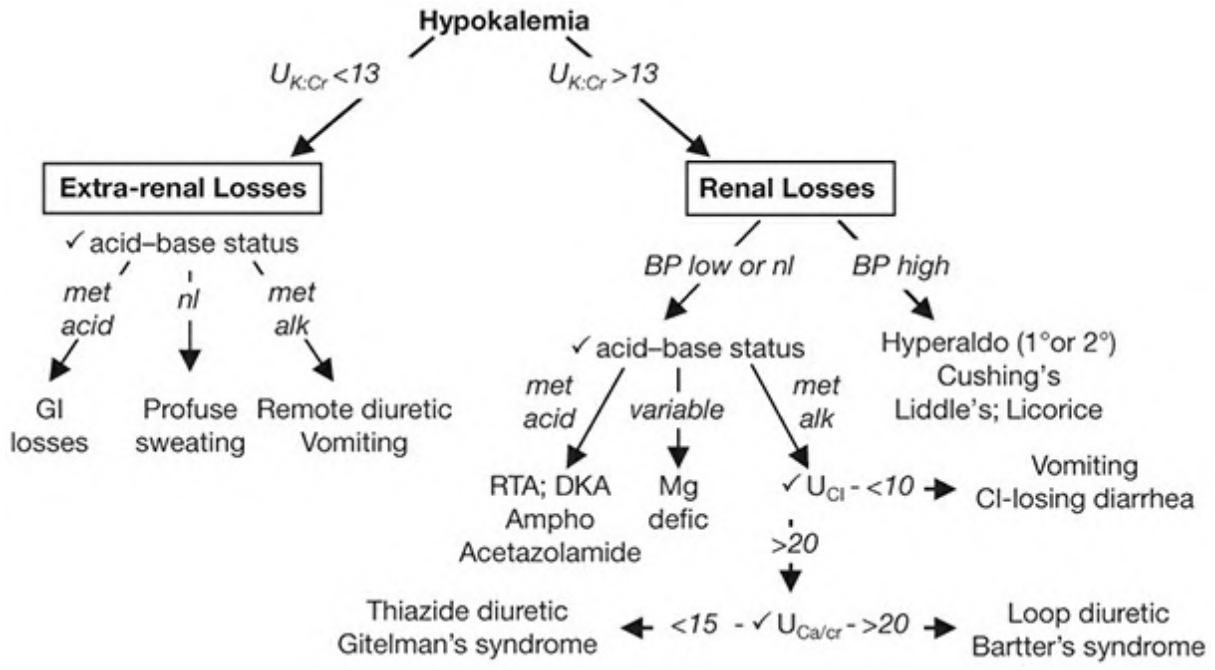
Clinical manifestations

- Nausea, vomiting, ileus, weakness, muscle cramps, rhabdomyolysis, ↓ insulin secretion
- Renal: ammoniagenesis, phosphaturia, hypocitraturia, NaCl & HCO_3 retention, polyuria
- ECG: may see U waves, ↑ QT, flat Tw, ST depression, ventricular ectopy (PVCs, VT, VF)

Workup (*JAMA* 2021;12:1216)

- Identify transcellular shifts & treat. TTKG validity questioned (*Curr Opin Nephrol* 2011;20:547).
- ✓ **$U_{K:Cr}$**: >13 mEq/g → renal loss; <13 mEq/g → extrarenal loss (*AJKD* 2019;74:682)
- If renal losses, ✓ **BP**, **acid–base**, **U_{Cl}** (U_{Na} unreliable), $U_{Ca/Cr}$, renin, aldosterone, cortisol

Figure 4-7 Approach to hypokalemia



Treatment (*NEJM* 2015;373:60 & 2024;390:1514)

- *If true potassium deficit:* **potassium repletion** (↓ 1 mEq/L ≈ 200 mEq total body loss) Dosage: 40 mEq PO q4h, 10 mEq/h (IV), 20 mEq/h (central line), 40 mEq in 1 L IVF
- Replete K^+ to >3 [>4 mEq/L if high-risk (HTN, CHF, arrhythmias, MI, digoxin, cirrhosis)]
- Beware of excessive potassium repletion if transcellular shift cause of hypokalemia
- Treat underlying cause (if ↓ vol: avoid dextrose as ↑ insulin → intracellular potassium shifts)
- Consider Rx that ↓ K loss: ACEI/ARB, K^+-sparing diuretics, βB
- Replete Mg if <2 mEq/L: IV Mg-SO_4 1–2 g q2h and oral Mg-oxide (limited by diarrhea)
  Causes of low Mg: GI loss (diarrhea, bypass, pancreatitis, malnutrition, PPI); renal loss (diuretics, nephrotoxic drugs, EtOH, ↑ Ca, 1° wasting syndromes, volume expansion)

Transcellular shifts (*BMJ* 2009;339:1019)

- Acidemia, ↓ insulin (DM), cell lysis (tumor, rhabdo, ischemic bowel, hemolysis, transfusions, resorbing hematomas, hyperthermia, rewarming), hyperkalemic periodic paralysis, ↑ osmolality. Drugs: succinylcholine, aminocaproic acid, digoxin, β-blockers.

Decreased GFR

- Any cause of oliguric or anuric AKI or any cause of end-stage renal disease

Normal GFR but with ↓ renal K excretion

- Normal aldosterone function
  - ↓ EAV (K excretion limited by ↓ **distal Na delivery & urine flow**): CHF, cirrhosis
  - Excessive K intake: in conjunction with impairment in K excretion or transcellular shift
  - Ureterojejunostomy (absorption of urinary K in jejunum)
- **Hypoaldosteronism:** same as etiologies of hypoaldo RTA (type IV)
  - ↓ renin: DM, NSAIDs, chronic interstitial nephritis, HIV, multiple myeloma, Gordon's
  - Normal renin, ↓ aldo synthesis: 1° adrenal disorders, ACEI, ARBs, heparin, ketoconazole
  - ↓ response to aldosterone Meds: K-sparing diuretics, TMP–SMX, pentamidine, calcineurin inhibitors Tubulointerstitial disease: sickle cell, SLE, amyloid, diabetes

Clinical manifestations

- Weakness, nausea, paresthesias, palpitations; Renal: ↓ NH_4^+ secretion → acidosis
- ECG: ST depression, peaked T waves, ↓ QT, ↑ PR interval, ↑ QRS width, loss of P wave, sine wave pattern, PEA/VF (ECG: low sens., cardiac arrest can be first manifestation!)

Workup (*Crit Care Med* 2008;36:3246)

- Rule out pseudohyperkalemia: falsely ↑ *measured* K due to cell lysis during blood draw (tourniquet, hemolysis, ↑ plt or WBC) or downstream of IVF w/ K; whole blood K more accurate than plasma K
- Rule out transcellular shift
- **Assess GFR**, if normal, then ✓U_K, U_{Na} (<25 mEq/d ↓ distal Na delivery). ⇒ $U_{K:Cr}$ (<13 favors ↓ renal K excretion).

Treatment of Hyperkalemia

Intervention	Dose	Onset	Comment
Ca gluconate **Ca chloride**[a]	1–2 amps IV	<3 min	Transient effect (30–60 min) Stabilizes cell membrane
Insulin	reg insulin 5–10 U IV + 1–2 amps $D_{50}W$	15–30 min	Peak 30–60 min, lasts 4–6 h ↓ K 0.5–1.2 mEq/L
Bicarbonate (esp. if acidemic)	1–2 amps IV 150 mEq in 1 L D_5W	15–30 min	Exchange K for H^+ in cells Lasts 5–6 h; ↓ K 0.7 mEq/L
β2 agonists	albuterol 10–20 mg inh. or 0.5 mg IV	30–90 min	Peak 90 min, lasts 2–6 h ↓ K 0.5–1.4 mEq/L (IV >inh)
K-binding resins	SPS[b] 15–60 g PO/PR patiromer 8.4–25.2 g/d PO Na zirconium 5–10 g PO	4–24 hrs hrs–d hrs	Exchange K for cations in gut (Na, Ca, H); ↓ K 0.8–1 mEq/L/d. Edema & HTN w/ Na zirconium.

Diuretics	furosemide ≥40 mg IV	30 min	↓ total body K
Hemodialysis	Most rapid in 1st hr (1 mEq/L)		↓ total body K (*JASN* 2017;28:3441)

[a]CaCl contains more calcium and is typically reserved for codes (↑ risk of tissue necrosis) or via central line

[b]~0.4% intestinal necrosis esp. postop, ileus, SBO/LBO, bowel disease (UC), renal txp (*Clin Nephro* 2016;85:38)

- *Rate of onset* important to note when establishing a treatment plan (*Mayo Clinic* 2020;96:744)
- **Stabilize** (initial): 10% CaCl (central) or gluconate (IV). ↑ memb. potential → ↓ excitability.
- **Redistribute**: insulin + dextrose (continuous if NPO), HCO_3, β_2-agonists
- **Eliminate**: SPS, patiromer, Na zirconium, diuretics (w/ saline if preserved renal fxn), consider emergent HD in life-threatening situations
- Patient information for diet education: http://www.kidney.org/atoz/content/potassium

KIDNEY DISEASE

Acute Kidney Injury (AKI) (*Lancet* 2025;405:241)

Definition (*KDIGO* 2012;2:1)

- **Stages in ICU correspond to** ↑ hospital mortality and LOS (*Crit Care Med* 2009;37:2552)
  Stage 1: Cr ≥0.3 mg/dL in 2 d or ↑ Cr ≥50%, or UOP <0.5 mL/kg/h for ≥6 h
  Stage 2: ↑ Cr 2–3× baseline in 7 d or UOP <0.5 mL/kg/h for ≥12 h
  Stage 3: ↑ 3× baseline in 7 d, UOP <0.3 mL/kg/h for ≥24 h, anuria ≥12 h, or Cr >4
- *Cannot* estimate GFR using Cr in setting of AKI or Δ'ing Cr (requires steady state)

Workup (*NEJM* 2014;371:55)

- **H&P:** meds, contrast, or other nephrotoxins; ↓ PO intake, HoTN, infxn/sepsis; trauma, myalgias; BPH/retention. Search for insult 24–48 hr prior ↑ Cr. VS, vol status, rash.
- **Urine evaluation:** output, urinalysis, **sediment**, electrolytes, and osmolality
- **Fractional excretion Na (FE_{Na})** = $(U_{Na}/P_{Na})/(U_{Cr}/P_{Cr})$; if diuretic, ✓ $FE_{UN}=(U_{UN}/P_{UN})/(U_{Cr}/P_{Cr})$
- Renal U/S or CT: r/o obstruction & cortical atrophy in chronic kidney disease
- Serologies (if indicated): see "Glomerular Disease"
- Renal biopsy (microscopy, IF, and EM): if etiology unclear (esp. if proteinuria/hematuria). Relative contraindic.: SBP >150, ASA/NSAID, anticoag, cirrhosis. DDAVP if GFR <45.

Etiologies and Diagnosis of Acute Kidney Injury (*Ann Inter Med* 2017;9:66)

Etiologies		UA, Sediment, Indices
Prerenal	↓ **Effective arterial volume** (*NEJM* 2007;357:797)| Hypovolemia, ↓ CO (CHF), ↓ oncotic pressure (cirrhosis/HRS, nephrotic), vasodilation (sepsis) Δ **local renal perfusion:** NSAIDs, ACEI/ARB, SGTL2i, contrast, calcineurin inhib, hyperCa **Large vessel:** RAS (bilateral + ACEI), VTE, dissection, abd compart. synd. (renal vs. compress),vasculitis	Bland Transparent hyaline casts FE_{Na} <1%, BUN/Cr >20 FE_{UN} ≤35%
Intrinsic	**Acute tubular necrosis (ATN)** *Severe ischemia, sepsis, CIN* (↓ RBF + toxin) *Toxins*	Pigmented granular muddy brown casts

	Drugs: vanc, AG, cisplatin, foscarnet, IVIG, pentamidine, amphotericin, tenofovir Pigments: Hb, myoglobin (*NEJM* 2009;361:62) Monoclonal: Ig light chains (*Blood* 2010;116:1397) Crystals: UA, ACV, MTX, indinavir, oral $NaPO_4$	± RBCs & protein from tubular damage FE_{Na} >2%, BUN/Cr <20 (except pigment, CIN) FE_{UN} >50%
	Acute interstitial nephritis (AIN) *Allergic:* β-lactams, sulfa drugs, NSAIDs, PPIs *Infection:* pyelo, viral, legionella, TB, leptospirosis *Infiltrative:* sarcoid, lymphoma, leukemia *Autoimmune:* Sjögren's, TINU, IgG4, SLE, ICIs	WBCs, WBC casts, ± RBCs w/ neg UCx ⊕ lymphs in NSAIDs
	Small-med vessel: chol emboli, PAN, TMAs (TTP, HUS, atypical HUS, DIC, preeclampsia, APS, malignant HTN, scleroderma renal crisis)	± RBCs ⊕ periph eos + ↓ C3/C4 in chol emboli
	Glomerulonephritis (see "Glomerular Disease")	Dysmorphic RBCs, RBC casts
Post	**Bladder neck:** BPH, prostate cancer, neurogenic bladder, anticholinergic meds **Ureteral** (bilateral or unilateral in single kidney): malig, LAN, retroperitoneal fibrosis, nephrolithiasis	Bland ± non-dysmorphic RBCs, WBC, crystals

General treatment (*CJASN* 2008;3:962)

- Prerenal: isotonic IVF ≈ alb (*NEJM* 2004;350:22). No clear benefit of balanced crystalloids (eg, LR) over normal saline (*NEJM* 2018;378:829 & 2022;386:815).
- Avoid nephrotoxic insults (meds and contrast); renally dose medications
- Optimize hemodynamics (both MAP & CO) and maintain euvolemia (*NEJM* 2007;357:797)
- *No* benefit to dopamine (*Annals* 2005;142:510), diuretics (*JAMA* 2002;288:2547), or mannitol

Managing complications

- May take 1–3 wk to recover from ATN; anticipate volume overload, ↑ K, ↑ PO_4, acidosis
- Episodes of AKI ↑ risk of CKD progression, even after recovery (*NEJM* 2014;371:58)
- Indications for urgent dialysis (when condition refractory to conventional therapy)
  - **A**cid–base: refractory acidemia (but not clearly superior to HCO_3 [*Lancet* 2018;392:31])
  - **E**lectrolyte disorder: hyperK; hyperCa, hyperPO_4, tumor lysis syndrome
  - **I**ntoxications (http://www.extrip-workgroup.org/): Poison Control (1-800-222-1222)
    Indicated for methanol, ethylene glycol, metformin, Li, valproic acid, salicylates, barb., theophylline, thallium. ? carbamazepine, APAP, dig, dabigatran.
  - **O**verload: refractory hypervolemia → hypoxemia (eg, CHF)
  - **U**remia: pericarditis, encephalopathy, bleeding
- Stage 3 AKI: wait until one of above indications or oliguria >72 hrs or ? BUN >112 mg/dL (*NEJM* 2016;375:122; *Lancet* 2020;395:1506). If oliguria >72 hrs, further delay until urgent indication ↑ mortality (*Lancet* 2021;397:1293).

Disease-Specific Management

Acute interstitial nephritis (AIN) (*CJASN* 2017;12:2046; *JASN* 2020;31:435)

- Commonly drug-induced: β-lactams, sulfa drugs, NSAIDs, PPIs, quinolones, allopurinol
- If suspected, prompt removal of offending drug; ? early steroids w/in 7 d of dx
- Rechallenging after suspected ICI-induced AIN may depend on oncology natural history

Cardiorenal syndrome (CRS) (*CJASN* 2017;12:1624)

- Multifactorial pathophys including: 1) ↓ CO, 2) ↑ renal venous congestion, 3) ↑ RAAS
- Bidirectionality: acute CHF → AKI, and oliguric AKI can worsen CHF (*JACC* 2008;52:1527)
- Rx: **IV loop diuretics** (bypass gut edema; dosing below); no diff. between high vs. low dose and bolus vs. gtt (*NEJM* 2011;364:797). No clinical benefit: dopa, nesiritide, ultrafilt.
- Prognosis: 7% ↑ mortality a/w each 10 mL/min ↓ eGFR in ADHF (*JACC* 2006;47:1987)

Contrast-induced acute kidney injury (CIAKI) (*NEJM* 2019;380:2146)

- Risk factors: CKD, DM, CHF, age, hypotension, ↑ contrast volume (*JACC* 2004;44:1393)
- AKI 24–48 h postcontrast, peaks 3–5 d, resolves 7–10 d (consider chol emboli if does not)
- Prevention: consider if eGFR <60 (espec. w/ proteinuria), DM, MI, HoTN (*CJASN* 2013;8:1618)
  Isotonic IV fluids: may be helpful if high risk (*Lancet* 2017;389:1312)
  Outpatients: 3 mL/kg/h × 1 h prior, 1–1.5 mL/kg/h × 6 h after (*JAMA* 2004;291:2328)
  Inpatients: 1 mL/kg/h × 6–12 h pre-, intra-, postprocedure (*Lancet* 2014;383:1814)
  Hold ACEI/ARB (*AJKD* 2012;60:576), NSAIDs, diuretics. Min. contrast & use iso-osmolar.
- Nephrogenic systemic fibrosis (NSF): fibrosis of skin, joints, internal organs ~2–4 wk post-gado exposure in CKD 4/5 with old class 1 agents. Class 2 agents carry minimal risk of NSF and lack evidence to support post-gado HD (*JAMA* 2020;180:223).

Hepatorenal syndrome (HRS; see "Cirrhosis"; *NEJM* 2021;384:818)

- Terlipressin 0.85 mg IV q6h (ideally, o/w norepi or vaso) for 3 d, then reassess SCr. ∅ if hypoxia. D/c if worsening resp. status or e/o coronary, periph, or mesenteric ischemia.

Obstructive diseases

- Dx: renal U/S if undifferentiated or CT abd/pelvic (I^-) if suspect nephrolithiasis
- Rx: Foley if urethra vs. perc. nephrostomy if above ureters, tamsulosin/finasteride
- Watch for post-obstructive diuresis after relieving blockage, replace ½ UOP w/ ½ NS.
  Hemorrhagic cystitis (rapid Δ in size of bladder vessels); avoid by decompressing slowly.

Polycystic kidney disease (*NEJM* 2008;359:1477 & 2017;377:1988)

- Mostly AD *PKD1/PKD2* mutations → renal cysts. PKD1 (85%) younger-onset ESRD.
- Rx: hydration, low-salt diet; tolvaptan reduces GFR decline. Family genetic screening.

Rhabdomyolysis (*NEJM* 2009;361:62)

- Pathophys: myoglobin-induced oxidant injury, vasoconstriction, myoglobin precipitation & prerenal (extravasation). Can lead to ↓ Ca, ↑ K, and ↑ PO_4.
- Diagnosis: UA ⊕ for heme but 0 RBCs (ie, myoglobinuria)
- Risk of AKI when CK >20,000. Rhabdo and mortality risk score: *JAMA Int Med* 2013;173:1821.
- Aggressive IVF (tailor IVF to target UOP ~3 mL/kg). If urine pH <6.5, consider $NaHCO_3$. ✓ K & Ca frequently, trend CK. Monitor for compartment syndrome.

Scleroderma renal crisis (*Nature Neph* 2016;12:678)

- 5–20% diffuse cutaneous SSc w/ narrowing glomerular vessels. Sx: renal failure, severe HTN, encephalopathy. Rx: max ACEi for BP control.

COVID-19-associated AKI (*Am J Physiol Renal Physiol* 2021;4:403)

- 17% of inPts. ATN >collapsing FSGS (high-risk *APOL1* genotype). ↑ clotting risk w/ RRT.

Thrombotic microangiopathies (TMAs): *see "Hematology"*

Chronic Kidney Disease (CKD)

Definition and etiologies (*Lancet* 2021;10302:786)

- **GFR** <60 for ≥3 mo *and*/*or* **kidney damage** (albuminuria, structural abnormality)
- Prevalence 15% in U.S.
- Albuminuria predicts all-cause & CV mortality, CKD progression (*NEJM* 2004;351:1296)
- Cr poor estimate of GFR, use equation (https://www.kidney.org/professionals/kdoqi/gfr_calculator) Cystatin-C-based formula less influenced by race than Cr-based (*NEJM* 2021;385:1737)
- Etiologies: DM (45%), HTN/RAS (27%), glomerular (10%), interstitial (5%), PKD (2%), congenital, drugs, myeloma, repeated insults (eg, Mesoamerican nephropathy)
- Progression to ESRD: kidney failure risk equation (*JAMA* 2016;315:164; kidneyfailurerisk.com)

Stages of CKD (With permission from *Kidney Int Suppl* 2013;3:1–150. Copyright © 2013 International Society of Nephrology.)

GFR Stage	GFR	Goals
1 (nl or ↑ GFR)	>90	Dx/Rx of underlying condition & comorbidities, slow progression; CV risk reduction
2 (mild)	60–89	Estimate progression
3a (mild–mod)	45–59	Evaluate and treat complications
3b (mod–severe)	30–44	Evaluate and treat complications
4 (severe)	15–29	Prepare for renal replacement therapy (RRT)
5 (kidney failure)	<15 or dialysis	Dialysis if uremic/volume overload; Txp

Albuminuria stage based on albuminuria (mg/d) or spot urine alb (mg) to Cr (g) ratio
Stages: A1 = <30 (normal/mild); A2 = 30–300 (moderate); A3 = >300 (severe)

Signs and Symptoms of Uremia (*NEJM* 2018;379:669)

General	Nausea, anorexia, malaise, uremic fetor, metallic taste, hypothermia
Skin	Uremic frost (white crystals in & on skin), pruritus, calciphylaxis
Neurologic	Encephalopathy (Δ MS, ↓ memory & attention), seizures, neuropathy, impaired sleep, restless leg syndrome
Cardiovascular	Pericarditis, atherosclerosis, HTN, CHF, cardiomyopathy (LVH)
Hematologic	Anemia, bleeding (due to platelet dysfunction and Epo deficiency)
Metabolic	↑ K, ↑ PO_4, acidosis, ↓ Ca, 2° hyperparathyroidism, osteodystrophy

Complications & treatment (*JAMA* 2019;322:1294; *KI* 2024;105:4S)

- **General:** renal referral when GFR <30 or proteinuria, access planning (avoid subclavian lines, preserve an arm by avoiding phlebotomy, BP measurements, IVs)

- **CV risk:** statin if age >50 (independent of ASCVD risk score), βB, etc.
- **Dietary restrictions:** Na (if HTN), K (if oliguric or hyperkalemic), PO_4, mod protein
- **Diabetes:** strict glc control; ACEI/ARB, SGLT2i, GLP-1RA (*NEJM* 2024;391:109), and MRA (if eGFR ≥25 & K nl) (*NEJM* 2020;383:2219 & 2021;385:2252) to slow CKD progression & ↓ risk of MACE & HF
- **BP control:** ideally <120/80, a/w ↓ mortality. ACEI or ARB, not both. For outPts, ✓ Cr & K in 1–2 wk, d/c if Cr ↑ 30% or K >5.4 (after dietary Δ & loop diuretic). No ▵ in eGFR if stop ACEI in late-stage CKD (*NEJM* 2022;387:2021).
- **SGLT2i:** if eGFR ≥20 and either DM or proteinuria. Transient ↓ in eGFR (<5) but then 30–40% ↓ risk of CKD progression & ↓ mortality (*NEJM* 2020;383:1436 & 2023;388:117).
- **Metabolic acidosis:** sodium bicarbonate or sodium citrate if low HCO_3 (*JASN* 2015;26:515)
- **Hyperkalemia:** 2-g K diet, see "Potassium Homeostasis"
- **Anemia:** goal Hb 10–11.5 g/dL, worse outcomes if target higher (*NEJM* 2009;361:2019)
  - epoetin (start 80–120 U/kg SC/wk) or darbepoetin (0.75 mg/kg q2wk)
  - iron supplementation to keep transferrin sat >20% (often given IV in HD Pts)
  - HIF-PHI (daprodustat) ↑ endogenous EPO production (*NEJM* 2021;385:2313 & 2325)
- **Uremic bleeding:** desmopressin (dDAVP) 0.3 μg/kg IV or 3 μg/kg intranasally
- **Uremic pruritus:** PO_4 control, antihistamines, SSRI, gabapentin, difelikefalin (opioid receptor agonist) if on HD (*NEJM* 2020;382:222)
- **2° hyperPTH:** ↑ PO_4, ↑ FGF-23, ↓ calcitriol, & ↓ Ca → ↑ PTH → renal osteodystrophy
  - Phosphorus binders (*take with meals!*) (*NEJM* 2010;362:1312). Non-Ca-based binders (eg, sevelamer) a/w ↓ mort. compared to Ca-based (*Lancet* 2013;382:1268).
  - Non-dialysis Pt: focus on modifiable factors (low PO_4 diet, Ca suppl., correct vit. D defic). In dialysis, wide target PTH range (2–9× ULN). Correct PO_4, then start vit. D (if 25-(OH)D <30) or 1,25-(OH)D analogue (calcitriol); stop if ↑ Ca (*KI* 2017;7:1).
  - Cinacalcet (parathyroid Ca-sensing receptor agonist) if ↑ PTH despite phosphorus binders ± vit. D analogue (*CJASN* 2016;11:161); consider parathyroidectomy
- **Calciphylaxis** (calcific uremic arteriopathy, *NEJM* 2018;378:1704)
  - Pathophys: calcification of media in dermal small- to med-sized blood vessels & SC fat → ischemia and skin necrosis w/ painful lesions (*NEJM* 2007;356:1049)
  - Risk factors: ESRD, ♀>♂, DM, vit. K def, obesity, warfarin, local trauma, thrombophilias
  - Dx: skin bx, but limitations (*Kidney Int* 2018;94:390); bone scan used in support of dx
  - Rx: wound care/debridement, ↓ PTH, d/c vit. D, Ca, warfarin (DOAC okay). Pain control, palliative care, ? Na thiosulfate. Prognosis: 60% 1-y mort. in ESRD (*AJKD* 2015;66:133).
- **Anticoag:** ESRD at ↑ bleed risk; if using DOAC, consider apixaban > rivaroxaban > dabigatran due to protein binding/renal clearance (*JASN* 2017;28:2241)
- **Transplant evaluation**

Diuresis

General considerations

- ↑ Na & H_2O excretion for treatment of HTN or edema in CHF, renal failure, and cirrhosis
- Daily wt most effective method of documenting successful diuresis

Loop diuretics (*NEJM* 2017;377:1964)

- **Drugs:** furosemide (Lasix), torsemide, bumetanide (Bumex), ethacrynic acid
- **Mech:** inhib NaK2Cl cotransporter in thick ascending limb (ThAL, site of 25% Na reabsorp) → ↓ medullary osmotic gradient & ↓ free H_2O reabsorption via ADH
  - Transient venodilation may aid in pulmonary congestion (*NEJM* 1973;288:1087)
  - Response is fxn of amt of drug excreted; ∴ ↑ dose needed in renal insufficiency, CHF
  - Sigmoidal dose–response curve; ∴ ↑ dose until induce diuresis, ↑↑ dose beyond that point yields diminishing returns compared with ↑ frequency of dosing
- **Dosing:** bioavailability PO furosemide ~50%, PO torsemide & bumetanide ~90%

40 mg IV = 80 mg PO Lasix = 20 mg PO/IV torsemide = 1 mg IV/PO bumetanide
Dose furosemide bid–qid; qd dosing can yield initial diuresis, but then anti-natriuresis. Cont. vs. bolus IV similar in acute CHF (*NEJM* 2011;364:797). Ethacrynic acid if sulfa allergy.
- **Adverse effects:** ↑ Na, ↓ K, ↓ Mg, ↓ Ca, hyperuricemia, ototoxicity, hypersensitivity (sulfa)

Thiazide diuretics (*JASN* 2017;28:3414)

- **Drugs:** hydrochlorothiazide (HCTZ), chlorothiazide (Diuril), metolazone (Zaroxolyn)
- **Mech:** inhib Na–Cl cotransporter in the distal convoluted tubule (DCT); 5% Na reabsorp
  synergistic with loop diuretic, esp. if chronic loop use
  ↓ effect when GFR <30, *except metolazone,* which is still effective in renal insufficiency
- **Dosing:** in theory, giving 30–60 min prior to loop diuretic would ↑ efficacy
- **Adverse effects:** ↓ Na, ↓ K, ↓ Mg, ↑ Ca, HLD, pancreatitis, ↑ glc, hypersensitivity

K-sparing diuretics (*NEJM* 2017;377:1964)

- **Drugs:** spironolactone, amiloride, triamterene, eplerenone, finerenone
- **Mech:** ↓ Na reabsorption (~1%) in collecting duct (amiloride/triamterene inhibit principal cell Na channel [ENaC]; spiro., eplerenone, & finerenone inhibit mineralocorticoid receptor).
  Relatively weak natriuretic activity, useful in combination with thiazide or in cirrhosis.
- **Adverse effects:** ↑ K (esp. w/ ACEI), metabolic acidosis, gynecomastia (spironolactone)

Approach to Diuresis (if inadequate diuresis, go to next step)	
Step	**Action**
1	**Loop diuretic PO:** ✓ response at 1–3 h, redose at 2× prior dose if needed
2	**Add thiazide diuretic PO** (potentiates response to loop diuretic)
3	**Loop diuretic IV:** bolus bid–qid ± thiazide (*may start here if inPt*) ↑ dose w/ ↑ Cr; initial effective IV Lasix dose ≈ 30 × Cr (ie, if Cr = 4 → 120 mg IV)
4	**Loop diuretic infusion:** bolus + continuous IV infusion ± thiazide (PO or IV)
5	**RRT:** consider ultrafiltration, CRRT, or HD

Disease state–specific regimens

- Renal insufficiency: loop diuretic (↑ dose to achieve effective delivery to ThAL) ± thiazide
- CHF: loop diuretic (↑ frequency over ↑ dose), IV for gut edema + thiazide (watch K & Mg)
- Nephrotic syndrome: urinary albumin binds secreted loop diuretic, use 2–3× normal dose
- Cirrhosis: spironolactone (blocks 2° hyperaldosteronism) + Lasix in 2.5:1 ratio
- Severe metabolic alkalosis: acetazolamide & treat underlying cause

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Renal Replacement and Dialysis

General (*NEJM* 2022;386:964; *JAMA* 2024;332:1559)

- Acute indications: see “AKI”; choices CRRT vs. HD
- Chronic indications: timing of RRT initiation should factor in Pt QoL, uremic sx, risk of development of urgent/acute indications; modalities PD vs. HD (no clear diff in outcomes)
- Outcomes of ESRD: death from CVD (50%), infxn (30%), withdrawal of care (20%)

Modalities			
	HD (Hemodialysis)	**CVVH** (Hemofiltration)	**PD**
Physiology	Diffusion	Convection	Diffusion

Access	AV fistula/graft or CVC	CVC	Peritoneal catheter
Prescription	Duration, volume goal; K, Na, Ca, HCO_3 in bath, anticoag	Volume goal, K & Ca in replacement fluid (HCO_3 vs. citrate)	PD fluid (dextrose, icodextrin), dwell time, # cycles
Complic.	HoTN, arrhythmia, disequilibrium syndrome* if very high BUN, ↑ CO HF	HoTN, ↓ PO_4, ↓ iCa (citrate toxicity in hepatic dysfxn)	Peritonitis, ↑ glc, ↓ albumin, R pleural effusion

*Disequilibrium syndrome: sx cerebral edema due to H_2O shifts after urea removal

Hemodialysis (HD) (*NEJM* 2010;363:1833)

- Solute removal across *semipermeable* membrane, countercurrent blood & dialysate flow
  Volume removal: Na/H_2O ultrafiltered via transmembrane pressure (TMP) gradient
  Solutes: Cr, urea, K diffuse from blood → dialysate; HCO_3 from dialysate → blood
  Solute removal inversely proportional to size; ∴ effective removal of K, urea, Cr, not PO_4
- 6× vs. 3×/wk improved HTN, LV mass, QoL, but ↑ vasc issues (*NEJM* 2010;363:2287); w/ 3×/wk HD, ↑ mortality risk during 2-d interval (Sa–Tu or Fri–Mo) (*NEJM* 2011;365:1099)
- Fever w/ catheter: empiric abx (vanc + GNR coverage qHD). GPC > GNR > mixed/fungal. Remove/replace catheter (depends on organism), "lock" abx (*JASN* 2014;25:2927).
- Central vein stenosis: assoc. with longer HD duration, tunneled catheters

Vascular Access		
	Advantages	**Disadvantages**
AV fistula	Highest patency Lowest risk of bacteremia Lowest mortality (*JASN* 2013;24:465)	Long maturation time (2–6 mo) Primary nonfunction (20%)
AV graft	Easier to create than AVF Maturation time (2–3 wk)	Poor 1° patency, often requiring thrombectomy or angioplasty
Catheter	Immediate use Use as bridge to AVF/AVG	Highest risk of bacteremia ↓ blood flow → ↓ HD efficiency

Continuous veno-venous hemofiltration (CVVH) (*NEJM* 2012;367:26)

- *Hemofiltration* rather than dialysis. Blood under pressure passes down one side *highly permeable* membrane filtering H_2O and solutes via TMP gradient (convective clearance); filtrate discarded. Replacement fluid infused (solute concentration similar to plasma, except no urea, Cr, PO_4). Fluid balance by adjusting filtrate/replacement fluid.
- Replacement fluid rate determines clearance. Choice of replacement fluid buffer:
  HCO_3 (+ heparin to prevent clotting, although can be run heparin-free)
  citrate: hepatically metabolized to HCO_3, ∴ cannot be given in cirrhosis/liver failure. Provides anticoag w/in machine via Ca chelation. Citrate toxicity: ↓ iCa but nl/ ↑ serum Ca and AG met acidosis.
  Dose adjust for solute and volume removal (*AJKD* 2016;68:645)
- Other CRRT modalities: CVVHD (dialysis; ↑ solute clearance, but ↑ cardiac stunning). CVVHDF (filtration & dialysis; combo of both) (*AJKD* 2016;68:645), AVVH/PIRRT (½ d Rx; good transition CRRT → iHD) (*AJN* 2020;51:318). No mort ▵ between CRRT modalities.
- Benefits compared w/ HD: ↓ gross fluid shift (preferred in HoTN), but slower clearance of solutes and toxins

Peritoneal dialysis (PD) (*JAMA* 2017;317:1864)

- Fluid removed via convection using oncotic pressure (eg, dextrose). ↑ concentrations and dwell times remove more fluid (less as glc equilibrates).
- PD fluid: dextrose (1.5%, 2.5%, or 4.25%), buffer (lactate), Na^+, Ca^{2+}, Mg^{2+}
- Infuse 10 min, dwell 90 min–5.5 h, drain 20 min; exchanges done manually or using cycler at night (automated or cont. ambulatory peritoneal dialysis APD, CAPD)
- PD peritonitis: abd pain & cloudy drainage (WBC >100 & >50% PMNs). 60–70% GPC, 15–20% GNR. Rx: abx IV or in PD, catheter removal for certain org (yeast, *Pseudomonas*).
- Sclerosing peritonitis, a rare long-term complication (*NEJM* 2002;347:737)
- Hyperglycemia: exacerbated by inflammation, long dwell times, and higher [glucose]
- Benefits: lower cost, independence, preservation of residual kidney function. No Δ mortality vs. HD (*AJKD* 2018;71:344).

Kidney transplantation (*Med Clin N Am* 2016;100:435)

- Refer when GFR <20. Contraindic: active malig, infxn, ischemia, noncompl, subst use
- 5-yr survival: living donor 91%; deceased donor 70–84% (*AJKD* 2016;23:281). Donors have minor ↑ risk of ESRD (*Am J Transplant* 2014;14:2434).
- Immunosuppression: calcineurin inhib (tacrolimus > CsA) or CTLA4 inhib (belatacept) (*NEJM* 2016;374:333), antimetabolite (MMF > AZA), prednisone, mTOR inhib (sirolimus) if others contraindicated
- Rejection: Ab (ABMR) or T-cell mediated (TCMR), a/w poor graft survival; BANFF criteria (*Am J Transplant* 2018;18:293). Rx options: ↑ immunosupp., pulse steroids, IVIG, rituximab.
- Late renal dysfxn: usual AKI causes + calcineurin tox, rejection (*NEJM* 2010;363:1451), BK virus, recurrence of 1° disease; usual w/u + immunosupp levels, donor-specific antigen (DSA), BK virus load, U/S, then bx if no other cause (*CJASN* 2008;3:S56 & 2011;6:1774)
- ↑ infxn (incl opportunistic such as CMV, JC, BK viruses; *CJASN* 2012;7:2058) & cancer (PTLD)
- ↑ CVD risk due to HTN (calcineurin inhib, RAS), DM & dyslipidemia (immunosupp meds)

GLOMERULAR DISEASE

GLOMERULONEPHRITIS (GN)

Definition (*Lancet* 2016;387:2036; *JASN* 2016;27:1278)

- ↑ glomerular inflammation → endothelial & podocyte injury
- Histology: proliferative (↑ cells), sclerosing (scar), necrotizing (areas cell death). Focal (<50% of glomeruli) to diffuse to crescentic. Segmental (<50% tuft) to global (100%).
- Clinically: hematuria w/ dysmorphic RBCs or RBC casts, ± subnephrotic proteinuria often w/ AKI, HTN, edema
- Progression: acute ≈ days; rapidly progressive (RPGN) ~6 wk; chronic ≈ mos; can be asx

ANCA ⊕ Vasculitis (Pauci-immune, Minimal Staining) ~40–45% of Total						
Pathogen: infxn, drug (hydral, allopurinol, contam cocaine) (*CJASN* 2017;12:1680)						
Disease	**Gran**	**Renal**	**Pulm**	**Asthma**	**ANCA Type[a]**	**ANCA ⊕**
Granulomatosis with polyangiitis[b]	⊕	80%	90% (+ ENT)	—	anti-PR3	90%
Microscopic polyangiitis	—	90%	50%	—	anti-MPO	70%
Eosinophilic gran with polyangiitis[b]	⊕	45%	70%	⊕	anti-MPO	50%

[a]Predominant type; can see either type (*NEJM* 2012;367:214); [b]GPA (Wegener's); EGPA (Churg–Strauss)

Anti-GBM Disease (Linear Staining) <15% of Total (*CJASN* 2017;12:1162)			
Disease	**Glomerulonephritis**	**Pulm Hemorrhage**	**Anti-GBM**
Goodpasture's	⊕	⊕	⊕
Anti-GBM disease	⊕	—	⊕

Immune Complex (IC) Disease (Granular Staining) ~40–45% of total (*CJASN* 2018;13:128)	
Renal-Limited Diseases	Systemic Diseases
Infection-related GN (*Staph* & *Strep*; ↓ C3, ± ASLO)	**SLE** (*CJASN* 2017;12:825) (⊕ ANA, ⊕ anti-dsDNA, ⊕ anti-Sm, ↓ C3, ↓ C4)
Membranoproliferative GN (MPGN) (↓ C3)	**Cryoglobulinemia** (⊕ cryocrit, ⊕ RF, ⊕ HCV, SPEP, ↓ C3, ↓ C4)
Fibrillary and immunotactoid GN (normal C3/C4)	**Endocarditis** (fever, ⊕ BCx, valvular disease, ↓ C3)
IgA nephropathy (normal C3, ±↑ IgA) (*NEJM* 2013;368:2402; *CJASN* 2017;12:677)	**Henoch–Schönlein purpura** (IgA nephropathy + syst. vasculitis w/ IgA deposits, nl C3, ±↑ IgA)

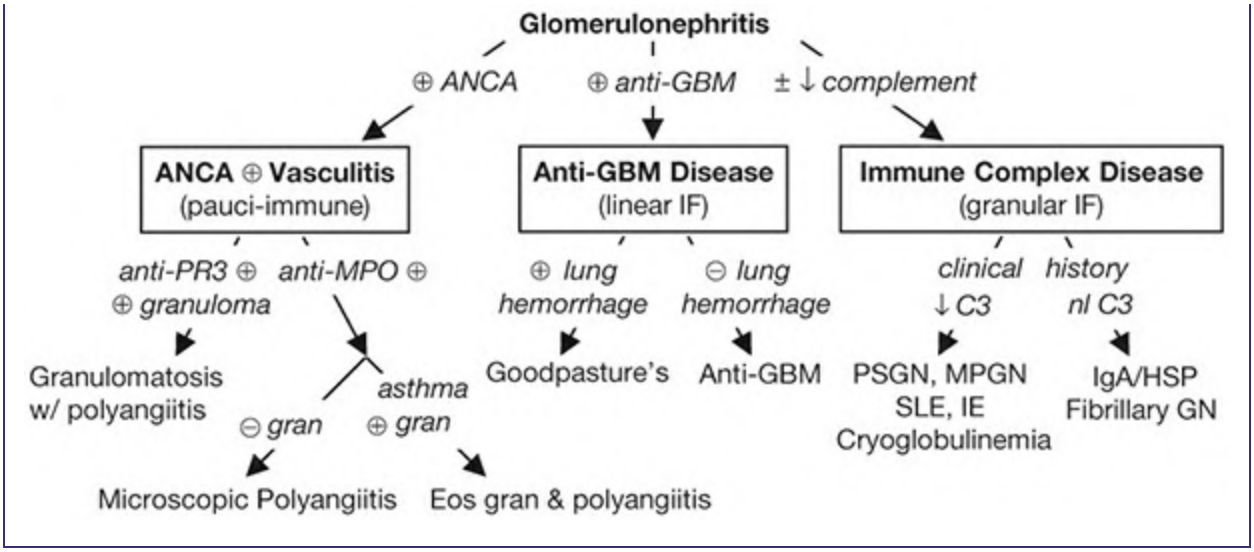
Oncology-related glomerulopathy (*CJASN* 2016;11:1681)

- Associations between malig (solid tumors & heme) and/or their Rx (HSCT & chemo-therapeutics) and GN, nephrotic syndrome, and thrombotic microangiopathies (TMA)
- Most common associations: membranous (solid tumors, HSCT), MCD (Hodgkin's, solid tumors), MPGN (CLL, MM), TMA (HSCT, VEGF, anti-EGFR, CNIs, TKIs, mTOR)
- **Monoclonal gammopathy of renal significance:** Ig-mediated kidney disease by nonmalignant B or plasma cells. Workup: SPEP, sFLC, flow cytometry, IFE, BMBx.

Workup (*JAMA* 2017;318:1276)

- *Acute GN/RPGN ± lung hemorrhage is an emergency* → requires early Dx and Rx
- UA + sediment (dysmorphic RBCs) ✓ ANCA, anti-GBM, C3/C4, SPEP, serum FLC
- Depending on hx: ANA, anti-dsDNA/Sm, RF, Hep B&C, HIV, ASLO, BCx, cryocrit, skin bx
- Consider GN mimics: thrombotic microangiopathies (qv), myeloma, AIN, cholesterol emboli
- Renal biopsy with immunofluorescence (IF) + electron microscopy (EM)

Figure 4-8 Approach to glomerulonephritis based on immunofluorescence pattern



Treatment (*AJKD* 2020;75:124 & 2020;76:265)

- If acute GN/RPGN suspected, give 500–1000 mg methylpred. IV qd × 3d *ASAP* while awaiting bx results
- SLE nephritis: induction w/ steroids + (cyclophosphamide [CYC] or MMF) ± (belimumab or CNI [voclosporin]) (*CJASN* 2017;12:825; NEJM 2020;12;383)
- ANCA ⊕ or anti-GBM: pulse steroids + CYC (or rituximab) ± avacopan. Plasma exchange if ⊕ anti-GBM. Controversial in ANCA ⊕ only, even w/ GN or pulmonary hemorrhage (*NEJM* 2020;382:622 & 2021;7:384).
- See "Vasculitis" for further disease-specific Rx details (eg, eculizumab for atypical HUS)

Asymptomatic Glomerular Hematuria

Definition and etiologies

- Hematuria ± proteinuria of glomerular origin w/o renal insufficiency or systemic disease (nonglomerular more common; see "Hematuria")
- Ddx: any cause of GN (esp. IgA); also consider Alport's (X-linked, deafness, renal failure), thin basement membrane nephropathy (autosomal dominant, benign; *JASN* 2013;23:364)

IgA nephropathy (*CJASN* 2017;12:677; *AJKD* 2021;78:429)

- Most common cause of GN; ♂ pred; peak incidence 20s–30s; can also be postinfectious
- Wide range of clinical presentations: asx hematuria (30–40%), gross hematuria ~1–3 d after URI (10–15%), chronic GN (10%), nephrotic syndrome (5%), RPGN (<5%)
- Though clinical presentation can be highly suggestive, definitive dx only w/ bx
- Prognosis: ↑Cr, HTN, proteinuria a/w poor prog. (*CJASN 2023;6:727*). 20–30% ESRD w/in 10 y.
- Rx: sparsentan (dual endothelin angiotensin receptor antagonist) preferred over ACEI/ARB; SGLT2i; oral budesonide or pred. (*Lancet* 2023;402:859 & 2077)

Nephrotic Syndrome

Definition (*JASN* 2014;25:2393)

- Podocyte injury (effacement) → loss of proteins (albumin, ATIII, Ig)
- Clinically: proteinuria >3.5 g/d, albumin <3 g/dL, edema, ↑ chol., VTE (25%), infection

Primary glomerular diseases (grouped by pathology)

- **Focal segmental glomerulosclerosis** (40%; *CJASN* 2017;12:502). Primary: permeability factor. Secondary: *adaptive* (hyperfiltration, sickle cell, obesity, anabolic steroids, OSA, ↑ protein, vesicoureteral reflux); *meds/toxins* (IFN, bisphosphonates, NSAIDs, heroin), *viral* (COVID-19, HIV) or genetic (*ApoL1* mutation in AA; *JASN* 2015;26:1443).
- **Membranous nephropathy** (30%; *CJASN* 2017;12:938, JASN 2021;32:268): Primary: Ab to PLA2R (70%), THSD7A (5%), other (EXT1-2, NELL1, Sema3B). Secondary: *infxn* (HBV, HCV, HIV, syphilis); *autoimmune* (eg, SLE); *carcinomas*; *drugs* (NSAIDs, penicillamine).
- **Minimal change disease** (20%, esp. children; *CJASN* 2017;12:332). Anti-nephrin Ab (*NEJM* 2024;394:422) allergies, NSAIDs, ampicillin, Hodgkin's disease, SLE, celiac dis.
- **Membranoproliferative GN** (5%, *mixed* nephrotic/nephritic features; *CJASN* 2014;9:600)
  - Immune complex mediated: infection (esp. HCV ± cryos, IE, HBV, "shunt" nephritis, other chronic infxns), SLE, cryos, Sjögren's, lymphomas, dysproteinemia, idiopathic
  - Complement mediated (rare); dense deposit disease (DDD), C3GN
- **Fibrillary-immunotactoid glomerulopathy** (1%; *JASN* 2008;19:34)
- **Mesangial proliferative GN** (? atypical forms of MCD/FSGS, 5%) IgM, C1q nephropathy

Systemic diseases with secondary glomerular involvement

- **Diabetes mellitus** (*CJASN* 2017;12:2032): nodular glomerulosclerosis (Kimmelstiel-Wilson lesion); glom. hyperfiltration → microalbuminuria → UA ⊕ → nephrotic range (10–15 y)
- **Amyloidosis:** AL or light-chain amyloid or AA amyloid secondary to inflammation
- **SLE** (*CJASN* 2017;12:825): typically membranous nephropathy (WHO class V)
- **Cryoglobulinemia** (*AJKD* 2016;67): a/w HCV, monoclonal gammopathy. Typically MPGN.

Workup (*BMJ* 2008;336:1185)

- U/A + sediment: usually benign; ± oval fat bodies ("Maltese crosses"; *NEJM* 2007;357:806)
- Measure proteinuria: 24-h urine or spot urine protein/Cr ratio (not accurate in AKI), renal bx
- 2° causes: ↑ Hb_{A1C} + retinop. → DM; ✓ ANA, anti-dsDNA, tox screen, C3/C4, SPEP/light chains, fat pad bx, cryocrit, HBV/HCV, HIV, RPR, APLA2R Ab, age-approp. CA screen

Treatment (*NEJM* 2013;368:10)

- General: protein suppl.; diuretics for edema; treat hyperlipidemia, Na restriction (<2 g/d)
- **ACEI/ARB/SGLT2i:** ↓ proteinuria → slow nonimmunologic progression of renal disease
- 1° glomerular: steroids ± rituximab or cytotoxic therapy (*CJASN* 2014;9:1386; *NEJM* 2019;381:36)
- Secondary causes: treat underlying disease
- Watch for malnutrition (protein loss), consider anticoag if albumin <2.5 in membranous (*KI* 2014;85:1412), infection (esp. encapsulated organisms b/c loss of immunoglobulins)

URINALYSIS

Urine Dipstick	
Metric	**Significance and Uses**
Specific gravity	Estimate U_{Osm}: each 0.001 above 1 ≈ 30 Osm (SG 1.010 → U_{Osm} ≈ 300) SG and U_{Osm} useful in evaluating AKI, dysnatremias, polyuria Heavy substances (glucose, contrast) ↑ SG more than U_{Osm}
pH	Range: 4.5–8.5; useful in evaluation of stones, RTAs, infection (urease UTI)

Protein	Detects albuminuria (>300 mg/d); see “Proteinuria”. False ⊖: dilute urine.
Blood	See “Hematuria”; ⊕ from RBCs, free Hgb, or free myoglobin (eg, rhabdo) False ⊕: semen, dilute urine (→ osmotic cell lysis), ↑ pH, vaginal blood False ⊖: vit. C
WBC	Suggests inflammation (UTI, interstitial nephritis, GN)
Ketones	Detects acetoacetate (ie, ketoacidosis) but *not* β-hydroxybutyrate
Leuk est	Lysed PMNs. Sn 80% for UTI. FN: proteinuria, glycosuria FP: ↓ pH or SG.
Nitrite	Suggests presence of nitrate reductase ⊕ bacteria (most enteric GNRs)
Bilirubin	↑ in biliary or hepatic disease
Glucose	⊕ in hyperglycemia (>180 mg/dL), pregnancy, Fanconi’s syndrome, SGLT2i

Urine Sediment (Microscopic Examination) (*Am J Kidney Dis* 2008;51:1052)	
Method: Centrifuge fresh sample (prox. port if Foley) × 3–5 min at 1500–3000 rpm; pour off supernatant in one motion; resuspend pellet by agitating base of tube; pour suspension onto slide w/ coverslip; view under “high dry” power; phase contrast for RBC morphology	
Cells	RBCs: assess amount & morphology (many dysmorphic → glomerular) WBCs: PMNs (UTI) vs. eosinophils (AIN; may require special stain) Epithelial cells: tubular (ATN), transitional (bladder or ureters), squamous
Casts *(see urinalysis photo inserts in appendix)*	*Proteins molded in lumen of renal tubule ± entrapped cellular elements RBC → GN* WBC → AIN, pyelonephritis, GN Granular (“muddy brown”): degenerating cellular casts → ATN Tubular cell → ATN Hyaline: Tamm–Horsfall protein (nonspecific) Waxy and broad → advanced chronic kidney disease
Crystals *(see urinalysis photo inserts in appendix)*	Calcium oxalate monohydrate: spindle, oval, or dumbbell shaped Calcium oxalate dihydrate: envelope shaped or octahedral Uric acid: variable shape; polychromatic under polarized light Cystine: hexagon shaped Struvite: coffin-lid shaped; seen in chronic UTI with urea-splitting organisms Drugs: sulfa, protease inhibitors: “shocks of wheat”; acyclovir: fine needles

Proteinuria

Etiologies of Proteinuria		
Category	**Description**	**Etiologies**
Glomerular (can be >3.5 g/d)	Disruption of filtration barrier → lose albumin	Glomerulonephritis Nephrotic syndrome
Tubulointerstitial (usually <1–2 g/d)	↓ reabsorption of freely filtered proteins → lose globulins	ATN; AIN Fanconi’s syndrome
Overflow	↑ production of freely filtered	Multiple myeloma

	proteins	Myoglobinuria
Isolated	By def'n: asx, normal renal fxn, sed, & imaging, no h/o renal disease	Functional (fever, exercise, CHF) Orthostatic (only when upright) Idiopathic (transient or persistent)

- **Urine dipstick**
  1+ ≈30 mg/dL, 2+ ≈100 mg/dL, 3+ ≈300 mg/dL, 4+ >2 g/dL; interpretation depends on SG; eg, 3+ in very concentrated urine might not indicate heavy proteinuria
  Insensitive for microalbuminuria and myeloma light chains (Bence–Jones protein)
- **Spot urine:** protein (mg/dL)/creatinine (mg/dL) ≈ g/d of proteinuria (*NEJM* 1983;309:1543) unlike urine dipstick, will accurately measure myeloma light chains reliable surrogate for 24-hr urine, esp. 1st morning void (*JASN* 2009;20:436); inaccurate if AKI depends on Cr production, ∴ underestimates if muscular, overestimates if cachectic
- **Moderate albuminuria** (30–300 mg/d *or* mg/L *or* mg/g Cr): early sign of glomerular vascular disease; marker for ↑ risk of CV adverse outcomes (*KI* 2013;3:19)
- Orthostatic proteinuria: typically in adolescents; ~90% of young ♂ with isolated proteinuria have orthostatic proteinuria; typically resolves spontaneously

Hematuria

Etiologies of Hematuria	
Extrarenal (far more common)	**Intrarenal**
Nephrolithiasis Neoplasm: transitional cell, prostate Infxn: cystitis, urethritis, prostatitis Foley trauma BPH *Schistosoma haematobium*	Nephrolithiasis or crystalluria Neoplasm Trauma/exercise Vascular: renal infarcts, renal v. thromb., sickle cell Glomerular: IgA, thin BM, others PKD (*NEJM* 2008;359:1477)

- Wide, overlapping ages for various etiologies, but general guide for common causes:
  <20 y: GN, UTI, congenital; 20–60 y: UTI, nephrolithiasis, cancer
  >60 y ♂: prostatitis, cancer, UTI; >60 y ♀: UTI, cancer

Workup (*NEJM* 2021;385:153)

- **Urine dipstick:** ⊕ if ≥3 RBCs; ⊕ dipstick and ⊖ sediment → myo- or hemoglobinuria
- **Urine sediment:** dysmorphic RBCs or RBC casts → GN → consider renal bx
- If suggestive sx, r/o UTI or nephrolithiasis
- Low cancer risk: repeat U/A in 4–6 wks; if still ⊕ → cystoscopy + imaging
- Intermediate risk (eg, ♂ 40–59 yrs or ♀ 50–59 yrs or 10–30 pack-yrs): cystoscopy + U/S
- High risk (eg, age ≥60 or >30 pack-yrs): CT urography (Se 96%, Sp 98%) + cystoscopy
- Rx: if obstruction: bladder irrigation and 3-way Foley on CBI

NEPHROLITHIASIS

Types of stones and risk factors (*Nat Rev Dis Prim* 2016;2:16008)

- **Calcium** (Ca oxalate > Ca phosphate): **70–90% of kidney stones** (*NEJM* 2010;363:954)
  Urine findings: ↑ Ca, ↑ oxalate (Ca-ox only), ↑ pH (Ca-phos only), ↓ citrate, ↓ volume
  2° hypercalciuria: 1° hyperparathyroidism, distal RTA, sarcoid, Li use
  2° hyperoxaluria: Crohn's, ileal disease w/ intact colon, gastric bypass, pancreatic insuffic.

Diet: ↑ animal protein, ↑ sucrose, ↑ Na, ↓ K, ↓ fluid, ↓ fruits/vegetables, ↑ vit. C, ↓ Ca
- **Uric acid:** 5–10% of kidney stones, radiolucent on plain film
  Urine findings: ↑ uric acid, ↓ pH (eg, from chronic diarrhea)
- **Magnesium ammonium phosphate** ("struvite" or "triple phosphate")
  Chronic upper UTI w/ urea-splitting organisms (eg, *Proteus, Klebs*) → ↑ urine NH_3, pH >7
- **Cystine:** inherited defects of tubular amino acid reabsorption

Clinical manifestations

- Hematuria (absence does not exclude diagnosis), flank pain, N/V, dysuria, frequency
- Ureteral obstruction (stones >5 mm unlikely to pass spont.) → AKI if solitary kidney
- UTI: ↑ risk of infection proximal to stone; urinalysis of distal urine may be normal

Workup

- **Noncontrast CT** 97% Se, 96% Sp (ureteral dilation w/o stone suggests recent passage); U/S (Se 57%, Sp 98%) may serve as initial test in stable patient (*NEJM* 2014;371:1100)
- Strain urine for stone to analyze; U/A & UCx; electrolytes, BUN/Cr, Ca, PO_4, PTH
- 24-h urine × 2 (>6 wk after acute setting) for Ca, PO_4, oxalate, citrate, Na, Cr, pH, K, vol.

Acute treatment (*JAMA* 2020;323:1961)

- Analgesia (narcotics ± NSAIDs; combination superior, *Ann Emerg Med* 2006;48:173), ensure adequate fluid repletion, antibiotics if UTI
- α-blocker >CCB to pass stone if ≤10 mm (*Cochrane* 2014:CD008509; *Lancet* 2006;368:1171)
- Indications for **immediate urologic eval and/or hosp:** obstruction (esp. solitary or transplant kidney), urosepsis, intractable pain or vomiting, significant AKI
- Urologic Rx: lithotripsy (*NEJM* 2012:367:50), ureteroscopic removal, lap/perc nephrolithotomy

Chronic treatment (*Am J Kidney Dis* 2023;82:617; *NEJM* 2023;388:781)

- Increase fluid intake (>2 L/d) for goal UOP 2 L/d (*J Nephrol* 2016;29:211)
- Calcium stones: 24-h urine identifies **specific urinary risk factors to treat**
  Diet: ↓ Na and meat (*NEJM* 2002;346:77), ↓ oxalate foods & sucrose/fructose
  Meds: thiazides (↓ urine Ca), K-citrate if low urine citrate, allopurinol if high urine uric acid
  Avoid low dietary Ca as ↑ oxalate absorp (*NEJM* 2002;346:77), unclear role of Ca suppl.
- Uric acid: fluid intake, urine alkalinization (K-citrate) to pH 6.5–7, allopurinol
- Magnesium ammonium phosphate (struvite): antibiotics for UTI; urologic intervention; acetohydroxamic acid; urease inhibitor reserved for experienced clinician, poorly tolerated
- Cystine: fluid, urine alkalinize (K-citrate) to 7–8, D-penicillamine, tiopronin (*KI* 2006;69:1041)

ANEMIA

↓ in RBC mass: Hct <41% or Hb <13.5 g/dL (men); Hct <36% or Hb <12 g/dL (women)

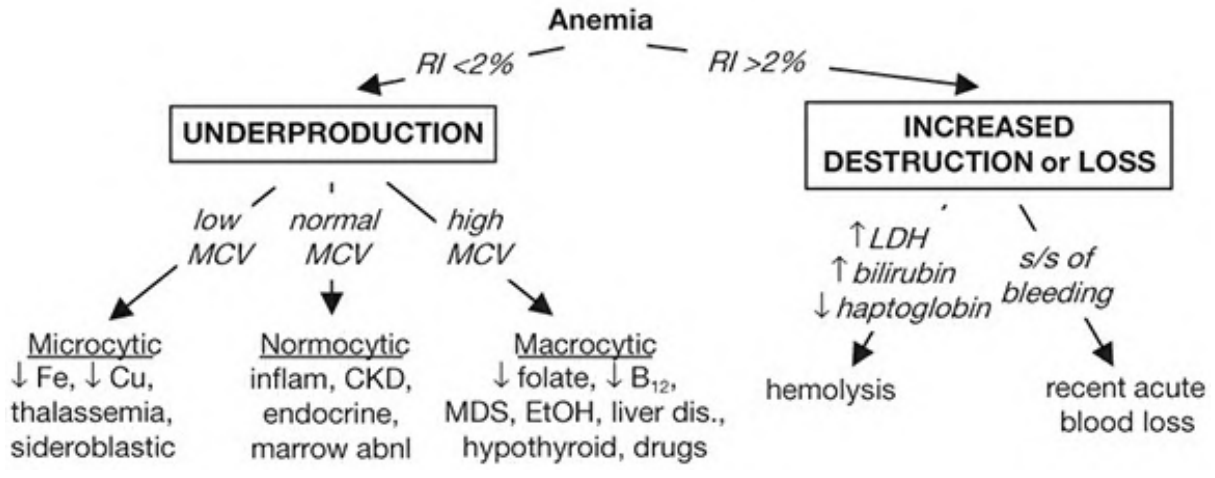
Clinical manifestations

- Symptoms: ↓ O_2 delivery → fatigue, exertional dyspnea, angina (if CAD)
- Signs: pallor (mucous membranes, palmar creases), tachycardia, orthostatic hypotension
- Other findings: **jaundice** (hemolysis), **splenomegaly** (thalassemia, neoplasm, chronic hemolysis), **petechiae/purpura** (bleeding or platelet disorder), **glossitis** (iron, folate, vitamin B_{12} defic.), **koilonychia** (iron defic.), **neurologic abnormalities** (B_{12} defic.)

Diagnostic evaluation

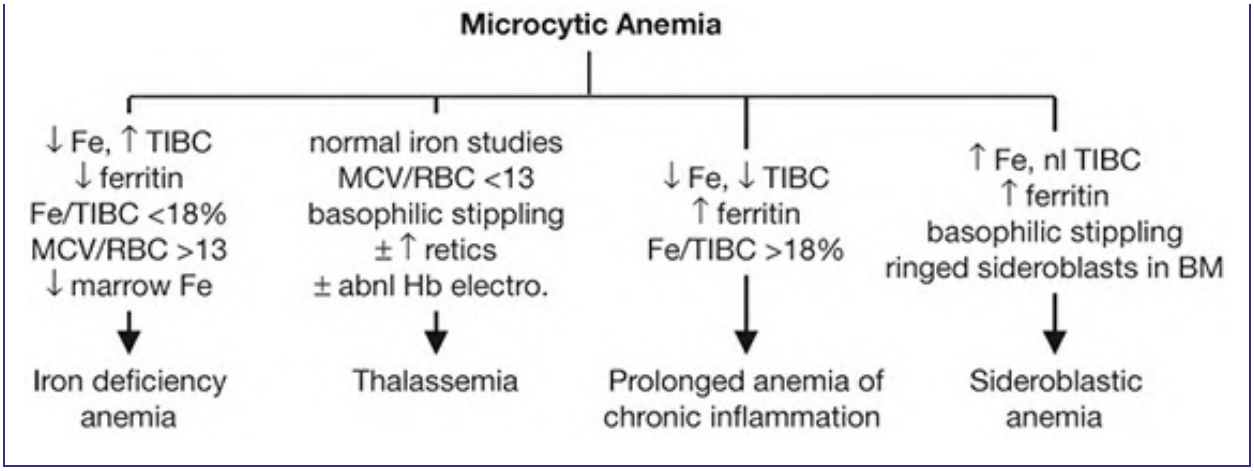
- History: bleeding, systemic illness, drugs, exposures, alcohol, diet (including **pica**), FHx
- CBC w/ diff.; RBC params incl. retics, MCV (nb, mixed disorder can → nl MCV), RDW
- **Reticulocyte index** (RI) = [reticulocyte count × (Pt's Hct/nl Hct)]/maturation factor maturation factors for a given Hct: 45% = 1, 35% = 1.5, 25% = 2, 20% = 2.5 RI >2% → adequate marrow response; RI <2% → hypoproliferation
- **Peripheral smear:** select area where roughly RBCs touch each other; ✓ RBC size, shape, inclusions (see "Appendix" & "Peripheral Smear"), WBC morphology, plt count
- Additional labs as indicated: hemolysis labs (if RI >2%, vide infra), iron/TIBC/ferritin, folate, B_{12}, LFTs, Cr, TFTs, Epo, Hb electrophoresis, enzyme/gene mutation screens
- **Bone marrow (BM) aspirate and biopsy (bx)**

Figure 5-1 Approach to anemia and common causes



Microcytic Anemias

Figure 5-2 Approach to microcytic anemias (*NEJM* 2014;371:1324)



Iron deficiency (*Lancet* 2021;397:233)

- ↓ marrow iron & depleted body iron stores → ↓ heme synthesis → microcytosis → anemia
- Fatigue and other sx can present before anemia. Look for mood change, hair loss, angular cheilosis, atrophic glossitis, pica (consumption of nonnutritive substances such as ice, clay), koilonychia (nail spooning).
- Plummer–Vinson syndrome (iron deficiency anemia, esophageal web & atrophic glossitis)
- Etiologies: **chronic bleeding** (GI [incl. cancer], menstrual, parasites, NSAIDs, etc.), ↓ **supply** (malnutrition; ↓ absorp. due to celiac sprue, Crohn's, ↑ gastric pH, subtotal gastrectomy), ↑ **demand** (preg; *Blood* 2017;129:940). Iron-refractory iron defic. anemia (IRIDA; rare genetic disorder due to hepcidin dysregulation; *Nat Genet* 2008;40:569).
- Diagnosis (eval ideally before Rx): ↓ **Fe**, ↑ **TIBC**, ↓ **transferrin sat** (Fe/TIBC), ↓ **ferritin** (espec. <30), ↑ plt. *Always consider workup for GIB*, incl. *H. pylori* serology. ? Celiac labs (**anti-TTG**, anti-endomysial IgA Abs).
- Treatment: oral Fe (~6 wks to correct anemia; ~6 mo to replete Fe stores). With severe anemia, persistent losses, prior to Epo Rx, or while inpatient, use *IV iron*. Nb, ferumoxytol can cause brighter signal on MRI, which can affect interpretation.

Thalassemias (*Lancet* 2022;399:2310)

- ↓ synthesis of α- or β-globin chains of Hb → ≠ subunits → RBC oxidative, membrane & structural damage; ∴ hemolysis + ineffective erythropoiesis
- α-**thalassemia** (*NEJM* 2014;371:1908): deletions in α-globin gene complex (nl 4 α genes), seen w/ Southeast Asian, Mediterranean, African, Middle East ancestry
  - 3 α → silent carrier; 2 α → α-thal minor = mild anemia, α-thal-1 (–/αα, milder) or α-thal-2 (-α/-α); 1 α → HbH (β_4) disease = severe anemia, hemolysis, and splenomegaly
  - 0 α genes → Hb Barts (γ_4) = intrauterine hypoxia and hydrops fetalis
- β-**thalassemia**: mutations in β-globin gene (nl 2 β-genes) → absent (β^0) or ↓ gene product (β^+) seen w/ Mediterranean (espec. Greek or Italian), African, or Asian ancestry
  - 1 mutated β-gene → thal minor (or trait) = mild anemia (no transfusions)
  - 2 mutated β-genes → transfusion-dependent (TDT) or non-transfusion-dependent (NTDT) depending on severity of mutations
- Jaundice from hemolysis, multiorgan damage from iron overload, cardiomyopathy, PHT, ↓ bone density, hepatosplenomegaly (extramedullary hematopoiesis), gallstones
- Dx: microcytosis, r/o iron deficiency. RBC can be nl despite anemia: **MCV/RBC <13** (Mentzer Index, 60% Se, 98% Sp), ± ↑ retics, basophilic stippling; **Hb electrophoresis** (nl in α-thal minor, ↑ A2 in β-thal minor), genetic testing.
- Treatment: transfusions if needed, folate for chronic hemolysis. Iron chelation. Consider luspatercept (blocks TGF-β superfamily ligand binding → ↓ SMAD signaling → erythropoiesis [*NEJM* 2020;382:1219]) and splenectomy. HSCT for severe disease. Gene Rx recently approved: exa-

cel (*NEJM* 2024;390:1663) & beti-cel (*Lancet* 2024;404:2175).

Sideroblastic anemia

- Defective heme biosynthesis within RBC precursors. Etiologies: **hereditary/X-linked** (*ALAS2* mutation most common), **idiopathic**, **MDS with ringed sideroblasts**, **reversible** (alcohol, lead, isoniazid, chloramphenicol, copper deficiency, hypothermia).
- Dx: MCV variable but narrows DDx of specific types; ↑ Tsat, ↑ ferritin, basophilic stippling, RBC **Pappenheimer bodies** (Fe-containing inclusions), **ring sideroblasts** (w/ iron-laden mitochondria) in BM, genetic testing
- Treatment: treat reversible causes; pyridoxine/thiamine depending on subtype; MDS-related Rx; supportive transfusions for severe anemia with iron chelation therapy

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Normocytic Anemias

Anemia of chronic inflammation (ACI; *NEJM* 2012;366:4)

- ↓ RBC production due to impaired iron utilization and functional iron deficiency from ↑ **hepcidin;** cytokines (IL-6, TNF-α) cause ↓ Epo responsiveness/production
- Etiologies: autoimmune disorders, chronic infection, inflammation, HIV, malignancy
- Dx: ↓ **Fe**, ↓ **TIBC (usually normal or low transferrin sat)**, ± ↑ **ferritin;** usually normochromic, normocytic (~70% of cases) but can be microcytic if prolonged
- Coexisting iron deficiency common. Dx clues include ↓ serum ferritin levels, absence of iron staining on BM bx, ⊕ response to a trial of oral iron and/or ↑ soluble transferrin receptor/ferritin index (*Am J Clin Pathol* 2012;138:642).
- Treatment: treat underlying disease ± iron and/or erythropoiesis-stimulating agent (ESA; eg, Epo). Iron if ferritin <100 or Fe/TIBC <20%. Consider ESA if Epo <500. Avoid ESA in cancer if treatment goal is cure (*Lancet* 2009;373:1532). Transfuse PRBCs only if symptomatic & insufficient time to wait for response to Epo or underlying disease Rx.

Anemias of other chronic disorders

- Anemia of CKD: ↓ Epo; treat w/ Epo & iron (see “Chronic Kidney Disease”)
- Endocrine deficiencies: hypometabolism and ↓ O_2 demand with thyroid, pituitary, adrenal, or parathyroid disease → ↓ Epo; can be normocytic or macrocytic

Pure red cell aplasia

- Destructive antibodies or lymphocytes → ineffective erythropoiesis
- Primary/idiopathic/autoimmune or secondary: LGL, CLL, autoimmune dx, parvovirus B19 and others, medications, thymoma, ABO-incompatible HSCT, anti-ESA antibodies
- Isolated severe anemia and ↓↓ reticulocytopenia
- Dx: **lack of erythroid precursors on BM bx**, other lines normal
- Treatment: treat underlying cause (thymectomy if thymoma). Spont recovery possible. If persistent, consider steroids, cyclosporine. IVIg if parvovirus and immunosuppressed (*Clin Infect Dis* 2013;56:968). Supportive care w/ PRBC transfusions; ? erythropoietin receptor agonist if due to antierythropoietin Ab (*NEJM* 2009;361:1848); consider HSCT.

Macrocytic Anemias

Megaloblastic anemia

- **Impaired DNA synthesis** → cytoplasm matures faster than nucleus → ineffective erythropoiesis and macrocytosis; due to **folate** or **B_{12} deficiency;** also in **MDS**
- ✓ **folate** and **vitamin B_{12}**; ↑ LDH & indirect bilirubin (due to ineffective erythropoiesis)

- Smear: **neutrophil hypersegmentation, macro-ovalocytes**, anisocytosis, poikilocytosis

Folate deficiency

- Folate present in leafy green vegetables and fruit; total body stores sufficient for **2–3 mo**
- Etiologies: **malnutrition** (alcoholism, anorexia, elderly), ↓ absorption (sprue), impaired metabolism (methotrexate, pyrimethamine, trimethoprim; *NEJM* 2015;373:1649), ↑ requirement (**chronic hemolytic anemia**, pregnancy, malignancy, dialysis)
- Diagnosis: ↓ folate; ↓ RBC folate, ↑ homocyst. but nl methylmalonic acid (unlike B_{12} defic.)
- Treatment: folate 1–5 mg PO qd for 1–4 mo or until complete hematologic recovery; *critical to r/o B_{12} deficiency first (vide infra)*

Vitamin B_{12} deficiency (*NEJM* 2013;368:149)

- B_{12} present only in foods of animal origin; total body stores sufficient for **2–3 y**
- Binds to **intrinsic factor** (IF) secreted by gastric parietal cells; absorbed in terminal ileum
  Etiologies: malnutrition (alcoholism, vegan), **pernicious anemia** (PA, autoimmune disease against gastric parietal cells, a/w polyglandular endocrine insufficiency, and ↑ risk of gastric carcinoma), other causes of ↓ absorption (gastrectomy, sprue, Crohn's, metformin), ↑ competition (intestinal bacterial overgrowth, fish tapeworm)
- Clinical manifestations: **neurologic** changes (**subacute combined degeneration**) affecting peripheral nerves, posterior & lateral columns of the spinal cord and cortex → numbness, paresthesias, ↓ vibratory & positional sense, ataxia, dementia, mood
- Dx: ↓ B_{12} (even low nl); ↑ homocysteine & methylmalonic acid; anti-IF Ab; ↑ gastrin in PA
- Treatment: 1 mg B_{12} IM qd × 7 d → qwk × 4–8 wk → qmo for life (oral if not PA) neurologic abnormalities are reversible if treated w/in 6 mos
  folate can reverse *hematologic* abnormalities of B_{12} deficiency but not *neurologic* changes
  (and can "steal" B_{12} stores → worsening of neuro complications)

Nonmegaloblastic macrocytic anemias

- **Liver disease:** often macrocytic, may see target cells, or spur cell anemia w/ hemolysis
- **Alcohol:** BM suppression & macrocytosis independent of folate/B_{12} defic. or cirrhosis
- **Other causes:** reticulocytosis; hypothyroid; MDS; meds impairing DNA synth (zidovudine, 5-FU, hydroxyurea, Ara-C); hereditary orotic aciduria; Lesch–Nyhan syndrome

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Pancytopenia

Etiologies and clinical manifestations

- Marrow infiltration/replacement: malignancy, infection (TB, fungal), storage disorder
- Marrow aplasia/failure: aplastic anemia, PNH, large granular lymphocytic leukemia, HLH, nutrition, alcohol, viral
- Destruction/consumption/redistribution: DIC, splenomegaly
- Anemia → fatigue; leukopenia → infections; thrombocytopenia → bleeding

Aplastic anemia (*NEJM* 2015;373:35)

- Epidemiology: 2–5 cases/10^6/y; biphasic (major peak in adolescents, 2nd peak in elderly)
- Diagnosis: pancytopenia w/ ↓ retics, BM bx w/ hypocellularity, usually nl cytogenetics
- Etiologies: **idiopathic** (½–⅔ of cases)
  Stem cell destruction: radiation, chemotherapy, chemicals (eg, benzene)
  Med rxn (eg, chloramphenicol, NSAIDs, sulfa drugs, gold, carbamazepine, antithyroid)
  Viruses (HHV-6, HIV, EBV, parvovirus B19); **post-viral hepatic failure** (not Hep A/B/C)

Immune disorders (SLE, GVHD post-HSCT, thymoma)
PNH (vide infra); Fanconi's anemia (congenital disorder w/ pancytopenia, macrocytic anemia, ↑ risk of MDS, AML, & SCC of head & neck, and multiple physical anomalies)
Shortened telomeres: seen w/ telomerase (*TERT, TERC*) mut. (10% of aplastic anemia), dyskeratosis congenita/DKC1 mut; a/w IPF, cirrhosis (*NEJM* 2009;361:2353)
Somatic mutations: PNH clones in ~50% of aplastic anemia (*Haematologica* 2010;95:1075)

- Rx & prognosis depend on severity & age. Supportive care w/ transfusions & infxn ppx.
  Moderate AA: consider HSCT, "triple immunosup. therapy" (IST, anti-thymocyte globulin, cyclosporine, eltrombopag), lower-intensity IST, or single-agent eltrombopag (TPO-RA)
  Severe and very severe SAA: HSCT if young or triple IST (*NEJM* 2022;386:11)

Myelodysplastic syndromes (MDS) (qv)

Paroxysmal nocturnal hemoglobinuria (PNH) (*Blood* 2021;137:1304)

- Acquired clonal stem cell disorder = inactivating somatic mutation of *PIG-A* gene → deficiency of GPI-anchor for CD55 & CD59 (inhib of complement) → complement- mediated RBC lysis, plt aggregation, & hypercoagulability
- Clinical: intravascular **hemolytic anemia**, **hypercoagulability** (venous > arterial; esp. intra-abdominal, cerebral), smooth muscle dystonias, **deficient hematopoiesis** (cytopenias); a/w aplastic anemia, MDS, and evolution to AML
- Dx: **flow cytometry** (↓ CD55 & CD59) on RBCs and granulocytes; urine hemosiderosis
- Treatment: supportive care (iron, folate, transfusions); consider anticoagulation
  C5 inhibitor (ravulizumab > eculizumab), alternative pathway inhibitor (iptacopan [*NEJM* 2024;390:994], danicopan [*Lancet Haematol* 2023;10:e955], pegcetacoplan). Monitor LDH for breakthrough hemolysis. Ensure vaccinations for encapsulated organisms.
  Allogeneic HSCT for severe bone marrow failure

Myelophthisic anemia (see also "Primary Myelofibrosis")

- Infiltration of bone marrow by cancer (commonly metastatic solid tumors), leukemia, infection, fibrosis (primary myelofibrosis), granulomas, lysosomal storage disorders

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Sickle Cell Disease

Genetics, pathophysiology, and diagnosis

- Recessive β-globin mutation → HbS polymerizes in setting of ↓ O_2 → membrane damage, cell dehydration, ↓ RBC deformability → **hemolysis** & **microvascular occlusion**
- ~8% African Americans heterozygotes ("sickle trait"; usually w/o sx); ~1/400 homozygotes (sickle cell disease)
- Dx: sickle-shaped RBCs and Howell–Jolly bodies on smear; Hb electrophoresis

Anemia

- Chronic hemolysis. Can be complicated by gallstones and iron overload.
- Acute aplastic crisis: often due to infxn, such as parvo. B19
- Splenic sequestration crisis, which can be c/b hypovolemic shock
- Hyperhemolytic crisis: triggered by transfusion or vaso-occlusion

Vaso-occlusive episodes

- Triggers: dehydration, infxn, Δ in weather, stress, menses, EtOH; but many w/o trigger
- Pain ± ischemia/infarction. Can lead to stroke, MI, acute chest syndrome (vide infra), VTE, renal papillary necrosis, avascular necrosis, dactylitis, priapism, retinopathy.
- General Rx: Pt-oriented analgesia (refer to acute care plan), IVF, VTE ppx, transfusion only if

atypical/more severe than usual (risk of alloimmunization + iron overload)

Acute chest syndrome

- Due to vaso-occlusion, infxn, atelectasis, thrombosis; also can be due to fat embolism
- Dx: pulmonary infiltrate on imaging plus any of: fever, hypoxemia, pulm sx
- Rx: RBC exchange if worsening/severe vs. simple transfusion. Abx for CAP coverage.

Infections

- Functional hyposplenism → bacteremia, meningitis, PNA, etc. from **encapsulated organisms**. Vaccinate against *Pneumo.*, *Meningo.*, *H flu*; also HBV.
- Infarcted bone → **osteomyelitis** (*Salmonella*, *Staph. aureus*)

Treatment

- Disease-modifying: hydroxyurea (↑ HbF); L-glutamine, crizanlizumab (P-selectin antagonist, withdrawn in Europe, poor efficacy). Gene therapy: Exa-Cel (↑ HbF expression), Lovo-Cel (replaces mutant β-globin mutation and replaces w/ fxnl copy [*NEJM* 2024;390:1649]).
- 1° indications for tfn: acute chest syndrome, CVA, multiorgan failure, sx anemia w/ Hgb 2 g/dL below baseline, surg ppx, acute sequestration, red cell aplasia

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Other Hemolytic Anemias

Causes of Hemolytic Anemia by Mechanism (*Lancet* 2000;355:1169 & 1260)			
Cause	**Mechanism**	**Examples**	**Mode**
Intrinsic	Enzyme deficiency	*G6PD* deficiency	**Hereditary**
	Hemoglobinopathies	Sickle cell anemia, thalassemia	
	Membrane abnormalities	Hereditary spherocytosis	
		PNH, spur cell anemia in liver disease	**Acquired**
Extrinsic	Immune mediated	Autoimmune; drug-induced, tx rxn	
	Traumatic	MAHA; prostheses (valves, TIPS)	
	Direct infections, toxins	Malaria, babesiosis; snake & spider venoms; Wilson's; hypotonic infusions	
	Entrapment	Hypersplenism	

Diagnostic evaluation

- ↑ retic count (RI >2%), ↑ LDH, ↓ hapto (83% Se, 96% Sp), ↑ indirect bili
- Autoimmune hemolysis: Coombs test = direct antiglobulin test (DAT) → ⊕ if agglutination occurs when antisera against IgG or C3 are applied to patient RBCs
- Location of hemolysis (many conditions can include components of both)
  - **Intravascular**: RBC destruction in vessels (shear by mech valve, DIC, toxins); assoc. w/ hemoglobinemia, hemoglobinuria, hemosiderinuria, ↑↑ LDH, ↓ haptoglobin
  - **Extravascular**: more common cause. Mϕ clear damaged/opsonized RBC; splenomegaly (reticuloendothelial expansion in spleen, liver, BM, LNs); ↑ LDH ↓ hapto.
- Family h/o anemia; personal or family h/o cholelithiasis

Red cell enzyme disorders (*Lancet* 2008;371:64)

- Most are autosomal recessive. Chronic hemolysis: DAT neg, RI >2%, ↑ LDH, ↓ hapto. Smear

variable; **Heinz bodies** (oxidized Hb) result in **bite cells** once removed by spleen.
- **G6PD deficiency**: X-linked. Most common in African or Mediterranean descent. Hemolysis precipitated by drugs (sulfonamides, dapsone, nitrofurantoin, rasburicase, primaquine, doxorubicin, methylene blue), infxn, DKA, foods (favism, *NEJM* 2018;378:60).
- **Pyruvate kinase deficiency**: ineffective glycolysis. Shift in Hb-O_2 dissociation curve; Pts tolerate anemia more than expected. Rx: PK activators (*NEJM* 2022;386:1432).

Hereditary spherocytosis (HS) (*Lancet* 2008;372:1411)

- Defect in cytoskeleton of RBC membrane (ankyrin, α- and β-spectrin, band 3, & pallidin)
- Most common in N. European populations (1/5000 births); ⊕ FHx (75% of Pts)
- Anemia, jaundice (mostly neonates), splenomegaly, pigmented gallstones
- Diagnosis: spherocytes on smear, ⊕ osmotic fragility test (~80% Se), ↓ eosin-5-maleimide (EMA) binding (93% Se; 99% Sp; *Haemat* 2012;97:516), acidified glycerol lysis test (Se 95%)
- Treatment: folate, transfusions, splenectomy for moderate and severe HS (balance w/ ↑ risk of future thrombosis and infection; *J Thromb Haemost* 2008;6:1289)

Paroxysmal nocturnal hemoglobinuria (vide supra)

Autoimmune hemolytic anemia (AIHA)

- Acquired, antibody-mediated RBC destruction
- **Warm AIHA: IgG** Abs opsonize RBCs *at body temp* → removal by spleen
  - Etiologies: idiopathic, lymphoproliferative (CLL, NHL), autoimmune (SLE), drugs, HIV, babesiosis (*NEJM* 2017;376:939)
  - Diagnosis: ⊕ **DAT IgG** (panagglutinin unlike alloantibody). Spherocytes on smear.
  - Treatment: steroids ± splenectomy, IVIg, cytotoxic agents, rituximab
- **Cold agglutinin disease: IgM** Ab binds to RBCs *at temp <37°C* → **complement fixation** → intravascular hemolysis and acrocyanosis on exposure to cold
  - Etiologies: idiopathic, lymphoprolif. disorders (eg, Waldenström's; monoclonal), ***Mycoplasma pneumoniae*** infxn, and infectious mononucleosis (polyclonal)
  - Diagnosis: ⊕ **DAT C3**, cold agglutinin titer, thermal amplitude. Agglutination on smear.
  - Treatment: sutimlimab (*NEJM* 2021;384:1323) or plasmapheresis if severe. Consider rituximab and/or bendamustine. Address underlying lymphoproliferative disorder.

Drug-induced hemolytic anemia

- Acquired, Ab-drug-mediated destruction vs. direct drug effect. Abx: ceph., sulfa drugs, rifampin, ribavirin. CV: methyldopa, procainamide, quinidine, thiazides. TCAs, phenothiazines, NSAIDs, sulfonylureas, MTX, 5-FU, rasburicase (G6PD defic.).
- Diagnosis: Coombs usually negative, ↑ LDH. Treatment: discontinue offending agent.

Microangiopathic hemolytic anemia (MAHA; *NEJM* 2014;371:654)

- Non-immune (Coombs neg) hemolytic anemia from intravascular red cell damage
- Etiologies: **thrombotic microangiopathies (TMA), disseminated intravascular coagulation** (**DIC**), malignancy, malignant HTN, eclampsia/HELLP, mech. cardiac valves, infected vascular prostheses
- Rx: see "DIC" section in "Coagulopathies" and "TTP/HUS" sections in "Platelet Disorders"

Hypersplenism

- Stasis/trapping in spleen → Mϕ attack/remodel RBCs → spherocytosis → hemolysis

Causes of Splenomegaly	
Etiology	**Comments**

RES hyperplasia	Hemolytic anemia, sickle cell disease, **thalassemia major**
Immune hyperplasia	Infxn [HIV, EBV, CMV, TB, **malaria**, **kala azar** ("black water fever" from visceral leishmaniasis), ***Mycobacterium avium*** complex], autoimmune disorders (SLE, RA w/ Felty's syndrome), sarcoidosis, serum sickness
Congestion	Cirrhosis, CHF, portal/splenic vein thrombosis, **schistosomiasis**
Infiltration (nonmalignant)	Lysosomal storage disorders (**Gaucher's**, Niemann–Pick), glycogen storage diseases, histiocytosis X, splenic cysts
Neoplasm	**MPN (CML, PMF, PV, ET), CMML, leukemia, lymphoma (NHL, HL, hairy cell leukemia, CLL, PLL, WM),** T-LGL, myeloma, amyloid

RES, reticuloendothelial system; **boldface** = causes of massive splenomegaly

DISORDERS OF HEMOSTASIS

Clinical Characteristics of Bleeding Disorders		
Feature	**Platelet/Vascular Defect**	**Coagulation Defect**
Site	Skin, mucous membranes	Deep in soft tissues (muscles, joints)
Lesions	Petechiae, ecchymoses	Hemarthroses, hematomas
Bleeding	After minor cuts: yes After surgery: immediate, mild	After minor cuts: unusual After surgery: delayed, severe

Figure 5-3 Approach to abnormal hemostasis (*NEJM* 2014;370:847)

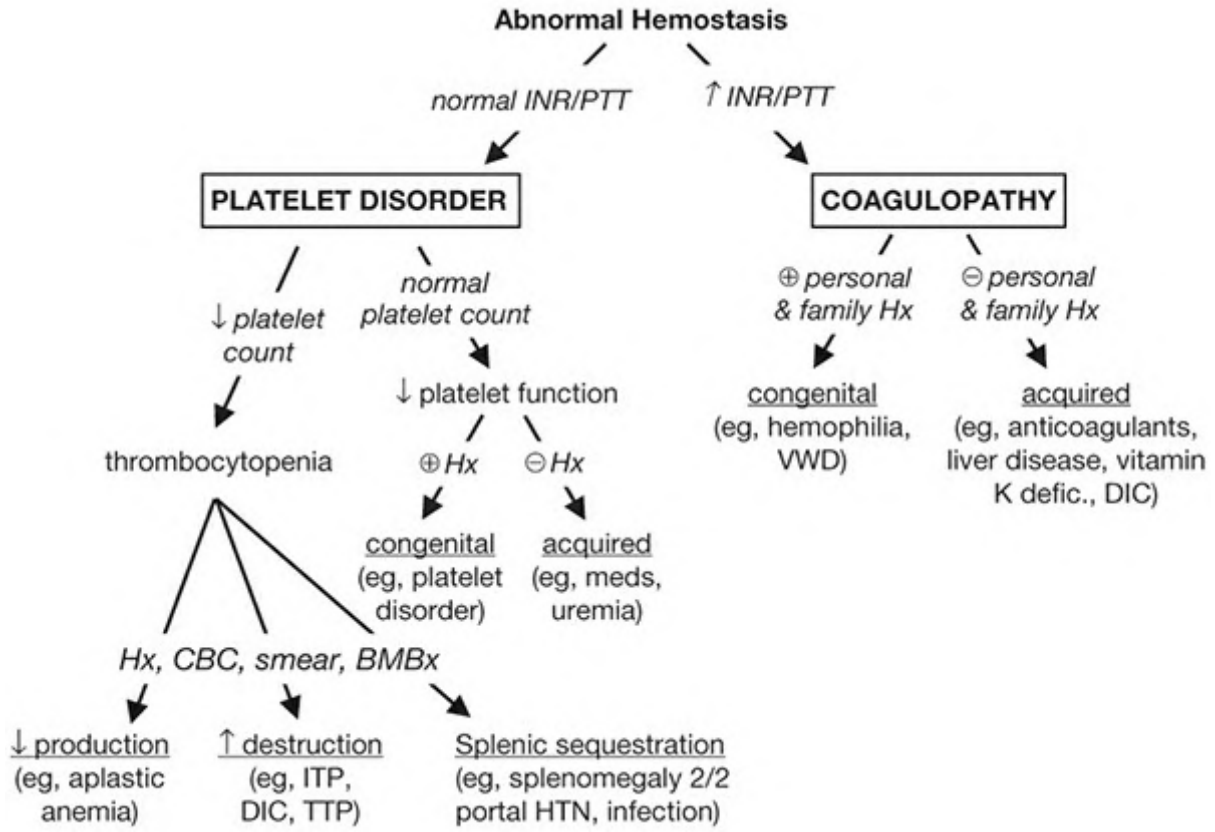
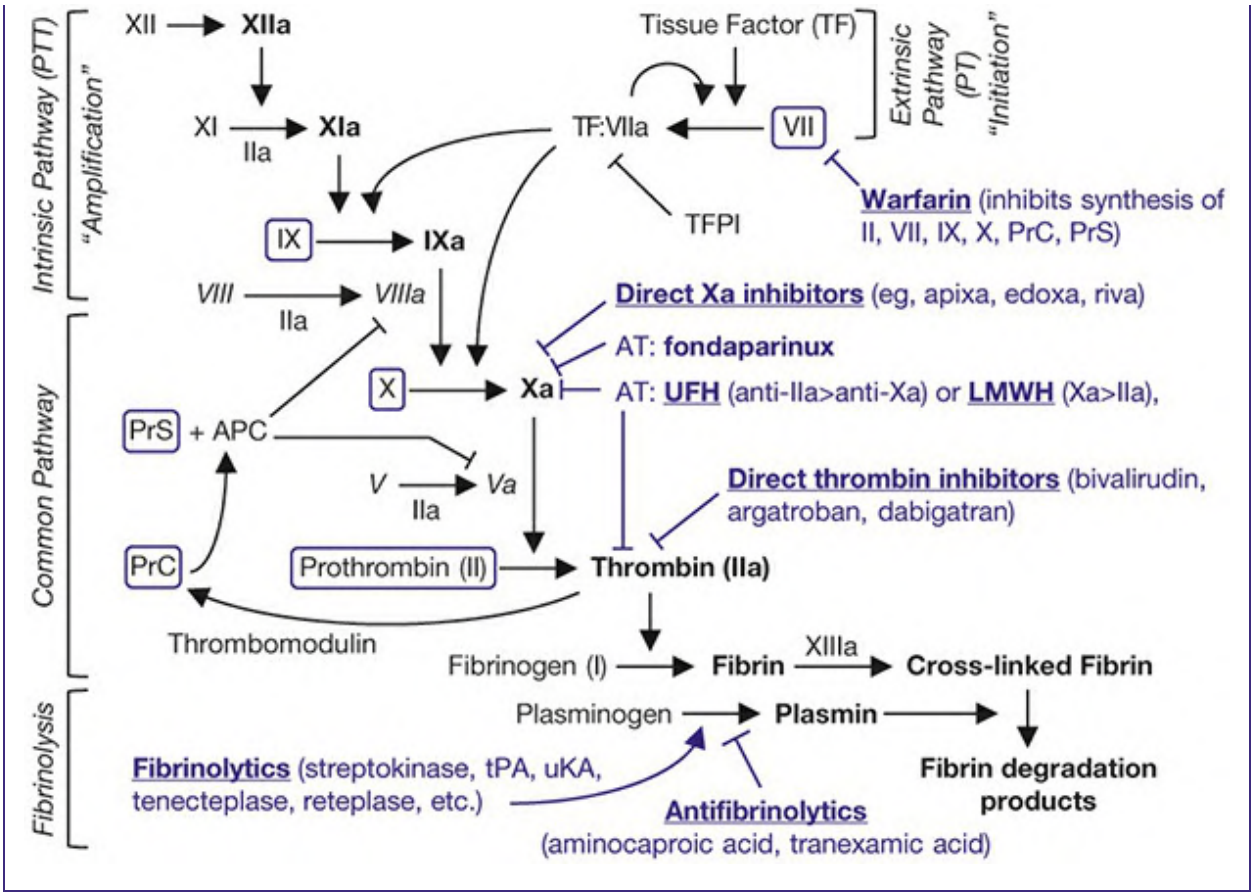


Figure 5-4 Coagulation cascade and pharmacotherapy (*NEJM* 2008;359:938)



APC, activ. protein C; AT, antithrombin; PrC, protein C; PrS, protein S; TF, tissue factor; TFPI, TF pathway inhib.

Vascular and connective tissue disorders

- Vitamin C deficiency: follicular hyperkeratosis, coiled hairs, gingivitis, musculoskeletal pain
- Hereditary hemorrhagic telangiectasia (HHT): telangiectasia + AVMs in lungs, GI tract, etc.
- Ehlers–Danlos: ± joint hypermotility; ± hyperextensibility of skin
- Osteogenesis imperfecta: bone fragility
- Vascular anomalies: Kasabach–Merritt, Klippel–Trenaunay

PLATELET DISORDERS

THROMBOCYTOPENIA (Plt count <150,000/µL)

Thrombocytopenia and Risk of Bleeding	
Platelet Count (cells/µL)	**Risk**
50,000–100,000	Risk with major trauma; can proceed with general surgery
<50,000	Risk with minor trauma or surgery
<20,000	Risk of spontaneous bleeding (less so with ITP)
<10,000	Risk of severe, life-threatening bleeding

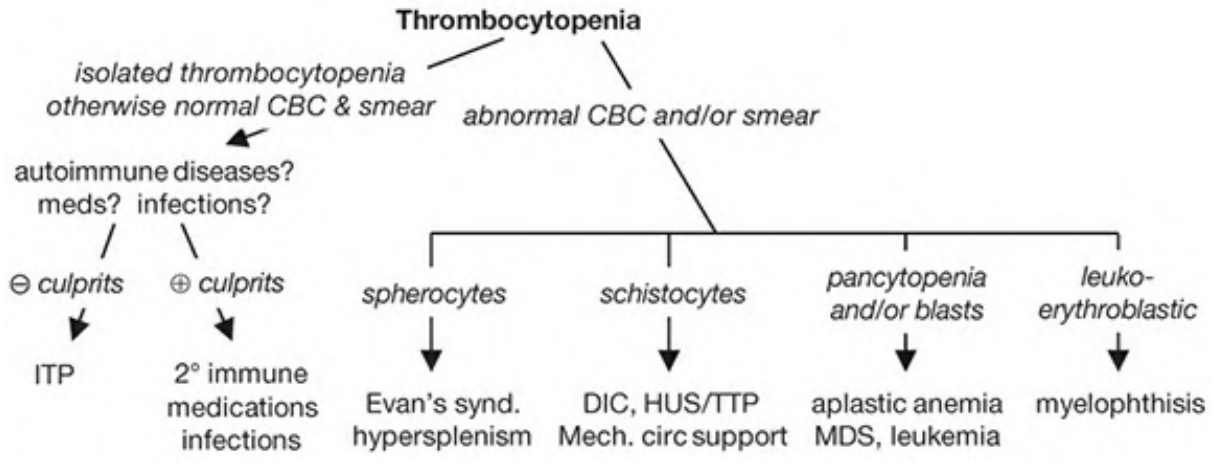
Etiologies

- ↓ **production**
  - **Hypocellular bone marrow:** aplastic anemia (qv), MDS, drugs (eg, thiazides, antibiotics, chemotherapy), alcohol, cirrhosis, viral infection
  - **Hypercellular bone marrow:** MDS, leukemia, severe megaloblastic anemia
  - **Marrow replacement:** myelofibrosis, hematologic and solid malignancies, granulomas
- ↑ **destruction**
  - **Immune-mediated** (distinguish primary from secondary; *Blood* 2009;113:2386)
    - 1° (idiopathic): immune thrombocytopenic purpura (**ITP**, vide infra)
    - 2°: infxn (**HIV**, **HCV**, HSV), collagen vascular dis. (**SLE**), APS, lymphoprolif. (**CLL**, lymphoma), drugs (*many*, including **heparin**, abciximab, quinidine, sulfonamides, vanco), alloimmune (posttransfusion), vaccine-induced
  - **Non-immune-mediated: MAHA** (DIC, HUS, TTP), ticlopidine/clopidogrel, vasculitis, preeclampsia/HELLP, cardiopulm bypass, CVVH, IABP, cavernous hemangioma, viral
- **Pregnancy:** commonly gestational thrombocytopenia (3rd tri) or ITP (1st tri or severe drop); multiorgan dsfxn or abnl CBC should trigger eval for preeclampsia HELLP, TMA, DIC
- **Abnormal distribution or pooling:** splenic sequestration, dilutional, hypothermia
- **Critical illness**: multifactorial (*Hematology Am Soc Hematol Educ Program* 2017;1:660)
- **Unknown:** ehrlichiosis/anaplasmosis, babesiosis, RMSF

Diagnostic evaluation

- H&P: meds, infxns, underlying conditions, splenomegaly, lymph nodes, **bleeding hx**
- **CBC with differential:** isolated thrombocytopenia *vs.* multilineage involvement
- **Peripheral smear** (r/o pseudothrombocytopenia due to platelet clumping)
  ↑ destruction → look for large plts, ↑ MPV, **schistocytes** (see "Peripheral Smear" inserts)
  ↓ production → rarely limited to platelets → look for **blasts**, hypersegmented PMNs, leukoerythroblastic Δs; can see inclusion bodies (*Anaplasma*), parasites (*Babesia*)
- Additional laboratory evaluations as indicated (eg, viral titers, flow cytometry, ANA) if anemia: ✓ reticulocyte count, LDH, haptoglobin, bilirubin to detect hemolysis if hemolytic anemia: ✓ PT, PTT, fibrinogen, D-dimer, Coombs, ANA BM bx for unexplained thrombocytopenia, espec. if associated with splenomegaly

Figure 5-5 Approach to thrombocytopenia



Immune thrombocytopenia (ITP) (*NEJM* 2019;381:945)

- Isolated thrombocytopenia due to immune plt *destruction* (auto-Ab to plts) & ↓ *production* (auto-

Ab to megakaryocytes) without precipitant

- Clinical manifestations: insidious onset of mucocutaneous bleeding; ♀:♂ = 3:1
- *Diagnosis of exclusion;* no definitive clinical or lab parameters, but typically:
  - CBC: isolated ↓ plt (<100,000/µL); 10% have ITP + AIHA = Evans syndrome
  - Peripheral smear: large platelets (not specific), r/o pseudothrombocytopenia
  - Poor response to platelet transfusions: increase <10 on 30-min post-CBC
  - BM bx: ↑ megakaryocytes, nl cellularity. Not required unless other abnl features or diagnostic uncertainty (*Blood* 2011;117:4910).
  - Evaluate for 2° ITP: HIV, HCV, lymphoprolif and autoimmune disorders
- Treatment: rarely indicated if plt >50,000/µL unless bleeding, trauma/surgery, anticoag

Treatment of ITP in Adults		
Approach	**Treatment**	**Notes**
First-line or upfront therapy	**Steroids:** prednisone 0.5–2 mg/kg/d PO tapered ~4 wk, or dexamethasone 40 mg PO × 4 d	↓ Mϕ FcR & ↓ anti-plt Ab 70–90% have initial response ~20% sustained remission
	IVIG[a] (1 g/kg/d IV × 2–3 d) *Consider if need rapid ↑ in plt in 24–48 hrs; lasts 2–6 wks*	Blocks Mϕ FcR, ↓ anti-plt Ab Interferes w/ Mϕ uptake Ab-coated plts; 80% have initial response
	Anti-Rh(D) Ig: alternative to IVIg if RBC Rh(D) ⊕; 50–75 µg/kg/d	Ab-coated RBCs overwhelm Mϕ FcR Avoid if h/o hemolysis; *not often used*
Second-line or maint. therapy	**Romiplostim**, **el/avatrombopag**	TPO-R agonists → ↑ plt prod
	Rituximab[a] (anti-CD20) ± dex	anti–B-cell Ab
	Splenectomy[b] *(less common)*	~65% long-term remission
	AZA, CYC, MMF	Immunosuppressants
	Danazol: 600 mg/d	Androgen (hirsutism) ↓ plt clearance
	Fostamatinib: 75–150 mg BID	Spleen tyrosine kinase (SYK) inhibitor
	Vinca alkaloids	Good initial response, less durable
Bleeding	Aminocaproic acid	Inhibits plasmin activation
	Methylprednisolone 1 g/d IV × 3 d	See above
	IVIG	See above
	Platelet transfusion	Given w/ IVIG or anti-Rh(D)

[a]✓ HBSAg & anti-HBc prior to rituximab and before IVIg (which could alter results)

[b]Post-splenectomy vaccinations needed (*Blood Adv* 2019;3:3829; *Eur J Haem* 2018;100:304)

Heparin-Induced Thrombocytopenias (*Chest* 2012;141:e495S; *NEJM* 2015;373:252)		
Feature	Type I **(not clin. signif)**	Type II **(clinically significant HIT)**
Mechanism	Direct effect of heparin (non-immune)	Immune (Ab)-mediated IgG against plt factor 4—heparin complex
Incidence	10–20%	1–3% with UFH, 0–0.8% LMWH
Onset	After 1–4 d of heparin therapy	After 4–10 d, but can occur in <24 h if prior exposure w/in 100 d (persistent Ab). Post-op highest risk. Can occur after heparin d/c.

Platelet nadir	>100,000/µL	~60,000/µL, ↓ >50%
Sequelae	None	Thrombotic events **(HITT)** in 30–50%
Management	Can continue heparin and observe	**Discontinue heparin** Alternative non-heparin anticoagulation

- Pathophysiology (type II): Ab binds heparin-PF4 → immune complex binds to plt → **plt activation**, further PF4 release → plt aggregates removed from circulation → **thrombocytopenia;** procoagulants released by plts and tissue factor released by endothelial cells damaged by HIT Abs → **prothrombotic state**
- Diagnosis
  - **Stepwise approach starting with 4T's:** ≤3 points → 99% NPV, investigate other causes; 4–5 points 22% PPV & 6–8 points 64% PPV, ✓ lab test & replace UFH

Evaluation of Suspected HIT ("4T's")			
Factor	**2 Points**	**1** Point	**0 Points**
Thrombo-cytopenia	↓ >50% *and* nadir ≥20k	↓ 30–50% *or* nadir 10–19k	↓ <30% *or* nadir <10k
Timing	5–10 d *or* ≤1 d if heparin w/in 30 d	5–10 d, >10 d *or* ≤1 d if hep w/in 30–100 d	≤4 d w/o recent hep
Thrombosis	New thromb, skin necrosis, acute rxn after IV UFH	Prog/recurrent thromb, suspect thromb or non-nec skin lesion	None
Other cause	None apparent	Possible	Definite

Labs: ⊕ HIT Ab using PF4-heparin ELISA or LIA, may confirm w/ functional plt assay (serotonin release) (>95% Se/Sp). With ↑ FP rate with HIT Ab, important to perform SRA in discordant situations, such as low 4T & ⊕ PF4 Ab or high 4T and ⊖ PF4 Ab.

Clinical context important: HIT Ab (esp. IgM ELISA) may be ⊕ in 10–20% of Pts on UFH/LMWH (*Am J Hem* 1996;52:90), up to 50% of cardiac bypass Pts (*Circ* 1997;95:1242)

- Rarely infections and adenovirus-based Rx can cause ⊕ PF4 Ab and s/s of "HIT"
- Treatment of HIT (type II) (*NEJM* 2015;373:252; *Blood Adv* 2018;2:3360)
  - **Discontinue heparin** *(incl. flushes, LMWH ppx, heparin lines).* Avoid plts (anecdotal link w/ thrombosis); if given warfarin, give vit. K to reverse, prevent warfarin skin necrosis.
  - **Nonheparin anticoag** (argatroban, bivalirudin, DOAC, fonda) *regardless of thrombosis;* if warfarin needed, start when plt >150k and overlap ≥5 d (*Blood* 2017;130:1104)
  - Screen all Pts for DVT w/ U/S. If ⊕ thrombosis (HITT): anticoagulate for ≥3–6 mo. If ⊖ thrombosis (HIT): give minimum 1 mo anticoag (most advocate for 3 mo); *25–50% thrombosis rate w/in 30 d.*
- H/o HIT: if PF4 Ab ⊖ or SRA ⊖ (typically >100 d after dx) → may consider reexposure to UFH (eg, for surgery); HIT recurrence low but can be seen (*Blood* 2014;123:2485)

Thrombotic microangiopathies (TMA; *NEJM* 2014;371:654; *Lancet* 2017;390:681)

- Endothelial injury → plt aggreg. & microvasc. thrombosis → ↓ plt & RBC hemolysis (MAHA)
- Dx: unexplained **thrombocytopenia** + **MAHA** ⊕ **schistocytes** (>2–3/hpf), ⊖ Coombs, normal PT/PTT & fibrinogen ↑↑ LDH (tissue ischemia + hemolysis), ↑ indirect bili., ↓↓ haptoglobin, ↑ Cr (esp. in HUS) Biopsy: arterioles filled with platelet hyaline thrombi Ddx: DIC, vasculitis, malignant hypertension, preeclampsia/HELLP syndrome

- **Thrombotic thrombocytopenic purpura (TTP)**
  Pathophys: ↓↓ ADAMTS13 protease activity (hereditary or autoAb) → ultralarge vWF multimers persist on endothelial surface → plt adhesion/aggregation → thrombosis
  Clinical sx (pentad, but all 5 not required and only seen in minority): ↓ plts + MAHA (100%) ± ΔMS (65%) ± renal failure (50%, less common and late finding) ± fever (25%)
  PLASMIC score to discriminate TTP from other TMAs (*Lancet Haematol* 2017;4:157)
  Rx: **urgent plasma exchange** ± glucocorticoids; FFP if delay, caplacizumab (avoid if bleeding risk; *NEJM* 2019;380:335), rituximab for 2° prevention (*Blood Adv* 2017;1:1159);
  plt transfusions contraindic. → ↑ microvascular thromb
- **Complement-mediated TMA** (CM-TMA) Pathophys: variant in complement genes or autoAb to CFH → ↑ complement activity Triggers: pregnancy, infection, surgery, inflammatory conditions Presentation: triad of MAHA + ↓ plts + AKI w/o preceding diarrheal illness Dx & Rx: r/o other TMA, ? empiric eculizumab or ravulizumab if severe renal dysfxn
- **Shiga Toxin–Mediated Hemolytic-Uremic syndrome (ST-HUS)**
  Pathophys: Shiga toxin damages renal endothelial cells → intrarenal thrombi
  Clinical: triad (MAHA + ↓ plts + AKI) + bloody diarrhea
  Rx: supportive care
- **Drug-induced TMA** (clinically similar to TTP; *Blood* 2017;129:2857)
  Immune mediated (Ab reacts w/ plts & endothelial cells): eg, quinine, gemcitabine
  Direct toxicity mediated: eg, gemcitabine, mitomycin, tacrolimus, CsA, bevacizumab

Disseminated intravascular coagulation (DIC): see "Coagulopathies"

Disorders of Primary Hemostasis: Platelet Function

Tests of platelet function

- **Platelet aggregometry**: aggregation in response to agonists (eg, ADP); numerous pre-analytic variables including plt count, meds (eg, NSAID, SSRI), sample handling
- Flow cytometry, electron micro., & genetic testing help confirm dx. PFA can screen if advanced testing unavailable.

Mechanisms and Etiologies of Platelet Function Abnormalities		
Function	**Inherited**	**Acquired**
Adhesion	Bernard–Soulier	Uremia
Aggregation	Glanzmann's thrombasthenia	$P2Y_{12}$ & GP IIb/IIIa inhib.; dysproteinemias
Granule release	Chediak–Higashi syndrome Hermansky-Pudlak syndrome	Drugs (ASA, NSAIDs); liver disease; MPN; cardiopulmonary bypass

Disorders of 1° Hemostasis: von Willebrand's disease (vWD) (*NEJM* 2016;375:2067)

- von Willebrand's factor (vWF) function = platelet adhesion & plasma carrier of factor VIII
- Most common inherited bleeding disorder. ~85% (type 1) have partial quantitative vWF defic., ~15% (type 2) qualitative defic., <1% (type 3) total/near-total absence of vWF.
- Acquired vWD: malig, MPN w/ ↑ plt count; autoimmune; hypothyroidism; drugs. Caused by different mechanisms (anti-vWF Abs, ↑ clearance, ↓ synthesis). Heyde's syndrome = vWF destruction by severe AS, a/w GI AVMs/bleed
- Diagnosis: ↓ **vWF:Ag**, ↓ **vWF activity** (ristocetin cofactor or GPIbM/R), normal propeptide ↓ **factor VIII**, ± ↑ PTT, ± ↓ platelets; **multimer analysis; genetic testing**
- For mild bleeds/prophylaxis: **desmopressin** (DDAVP) for Type 1 if prior efficacy challenge done. Plt tfn, antifibrinolytics (eg, TXA). For severe bleed → vWF concentrate.

Uremic bleeding

- Uremia → platelet dysfunction including ↓ aggregation, impaired adhesiveness
- Treatment: **DDAVP**, cryoprecipitate, correct anemia (↑ plt flow to edge of vessel wall and interaction with endothelium), consider holding anti-plt agents

COAGULOPATHIES

Screening Test Abnormalities in Inherited and Acquired Coagulopathies				
PT	**PTT**	**Factors**	**Inherited**	**Acquired**
↑	↔	VII	FVII defic.	**Vit. K defic.; liver dis.;** factor inhib.
↔	↑	VIII, IX, XI, XII	Hemophilias, vWD	**Antiphospholipid Ab;** factor inhib.
↑	↑	I, II, V, or X	Fbgn, FII or FV defic.	**DIC; liver dis.;** factor inhib.

Further coagulation tests (*JAMA* 2016;316:2146)

- Mixing study: useful if ↑ PT or PTT; mix Pt's plasma 1:1 w/ normal plasma and retest
  PT/PTT normalizes → factor **deficiency;** PT/PTT remains elevated → factor **inhibitor**
- Coagulation factor levels: useful if mixing study suggests factor deficiency
  DIC → all factors consumed; ∴ ↓ factors V and VIII
  Liver disease → ↓ all factors *except* VIII; ∴↓ factor V, normal factor VIII
  Vitamin K deficiency → ↓ factors II, VII, IX, X (and protein C, S); ∴ normal V and VIII
- **DIC screen:** ↓ fibrinogen (consumed), fibrin degradation products (FDPs, ⊕ from intense fibrinolysis), ↑ D-dimer (more specific FDP test that detects degradation of X-linked fibrin)

Hemophilias (*Lancet* 2025;405:736)

- X-linked recessive **factor VIII** (hemophilia A) or **factor IX** (hemophilia B) **defic. or inhib.**
- Classification: mild (5–25% normal factor activity), moderate (1–5%), or severe (<1%)
- Clinical manifestations: hematomas, hemarthroses, bruising, bleeding (mucosal, GI, GU)
- Diagnosis: ↑ PTT (normalizes w/ mixing study), nl vWF, ↓ VIII/IX, genetic test. Screen for inhibitor particularly if prior factor received and if tfn becomes ineffective.
- Acute bleed: If minor → antifibrinolytics (eg, TXA) ± desmopressin (if Hem A). Otherwise, factor VIII/IX. If inhibitor, use bypassing agent (rVIIa).
- Prophylaxis if prior bleeds or <1%: traditional or extended half-life factors (*NEJM 2023;388:*310); emicizumab (bridges factor IX & X) for hemophilia A w/ & w/o inhibitors (*NEJM* 2017;377:809 & 2018;379:811); still need to treat severe bleeds. Avoid FEIBA w/ emicizumab (TMA risk).
- Gene therapies recently approved (*NEJM* 2023;388:694 & 706; 2024;391:1108)

Coagulation factor inhibitors (anti-factor antibodies; anti-factor VIII most common)

- Etiologies: hemophilia; postpartum; lymphoproliferative & autoimmune disorders; cancers
- Diagnosis: ↑ PTT (does *not* normalize w/ mixing study); Bethesda assay quantitates titer
- Rx: if high titer → **recomb. factor VIIa**, porcine factor concentrates, activated prothrombin complex; for others → high-purity human recomb. factor, plasmapheresis, immunosupp.

Disseminated intravascular coagulation (DIC) (*NEJM* 2014;370:847)

- Etiologies: trauma, shock, infection, malignancy (esp. APL), obstetric complications
- Pathogenesis: *massive* activation of coagulation that overwhelms control mechanisms
  Thrombosis in microvasculature → ischemia + microangiopathic hemolytic anemia
  Acute consumption of coagulation factors and platelets → **bleeding**

Chronic DIC → able to compensate by ↑ factors and platelets → **thrombosis**

- Diagnosis: ↑ PT, ↑ PTT, ↓ **fibrinogen** (may be *nl* b/c acute phase), ⊕ **FDP/D-dimer**, ↓ plts, ⊕ schistos, ↑ LDH, ↓ hapto; *chronic* DIC: ⊕ FDP/D-dimer, variable plts, other labs nl
- Treatment: Rx underlying process; support w/ **FFP**, **cryo** (goal fbgn >100 mg/dL) & **plts**

Vitamin K deficiency

- Etiologies: malnutrition, ↓ absorption (antibiotic suppression of vitamin K–producing intestinal flora or malabsorption), liver disease (↓ stores), warfarin

Properties and Antidotes for Anticoagulants & Fibrinolytics (*Circ* 2016;134:248)			
Anticoag.	**$t_{1/2}$**	**Labs**	Rx for O/D w/ Serious Bleeding (+ d/c anticoag)
UFH	60–90′, RES	↑ PTT	**Protamine** IV 1 mg/100 U UFH (max 50 mg). For infusions, dose to reverse 2× UFH given per h.
LMWH	2–7°, K	anti-Xa*	Protamine reverses ~60%. 1 mg per 1 mg enox.
Bivalirudin	25′, K	↑ PTT	Dialysis
Argatroban	45′, L	↑ PTT	? Dialysis
Warfarin	36°, L	↑ PT	*No bleeding:* vit. K 2.5 mg PO if INR >9, o/w no e/o clinical benefit (*Blood Adv* 2019;3:789) *Bleeding:* **vit. K** 10 mg IV + either 4F-PCC (KCentra, 25, 35, or 50 U/kg for INR 2–4, 4–6, or >6) or **FFP** 2–4 U IV q6–8h (slower, more volume)
Fibrinolytic	20′, LK	↓ fbgn	**Cryo**, **FFP**, ± tranexamic or aminocaproic acid
Dabigatran	~12°, K	↑ PTT*	Idarucizumab: mAb binds drug (*NEJM* 2017;377:431)
Rivaroxaban Apixaban Edoxaban	8–12°, K > L	↑ PT* anti-Xa*	Andexanet: 800 mg bolus (30 mg/min) → 8 mg/min infusion × 2 hr (½ of above if taking ½ dose DOAC or ≥8 hrs since last dose). 4F-PCC if no andexanet.

*Routine monitoring not performed. Mode of excretion: K, kidney; L, liver; RES, reticuloendothelial system. 4F-PCC: prothrombin complex concentrate (FII, VII, IX, X; Protein C & S). Anti-fibrinolytics: tranexamic, aminocaproic acid.

HYPERCOAGULABLE STATES

Suspect in Pts with venous (rarely arterial) thrombosis at young age or unusual locations, recurrent thromboses or pregnancy loss, or ⊕ FHx

Inherited Thrombophilias			
Risk Factor	**Prevalence**	**VTE***	**Comments**
Factor V Leiden	~5%	~5	Activated protein C (APC) resistance
Prothrombin mutation	2%	~4	G20210A → ↑ prothrombin level

Protein C deficiency	0.02–0.05%	>20	Warfarin-induced skin necrosis risk
Protein S deficiency	0.01–1%	>20	
Antithrombin III def.	0.04%	>20	May be heparin resistant

*Relative risk of first VTE compared to patient w/o respective thrombophilia

Acquired thrombophilias

- If splanchnic thrombosis or cerebral venous sinus thrombosis, consider testing for MPN (*JAK2 V617F*) and PNH (flow cytometry for CD55, CD59)
- If arterial thrombosis without clear risk factors or unusual location, consider APS (vide infra)
- Age-appropriate malignancy screening (occult cancer in ~4% of initial unprovoked VTE; no benefit of routine abd/pelvis CT; *NEJM* 2015;373:697)

Approach to thrombophilia testing (*Blood Adv* 2023;7:7101)

- Avoid sending at initial thrombosis diagnosis. Typically does not change management & testing confounded in short term by consumption during thrombosis and various a/c.
- Once initial treatment is complete (3–6 mos), consider whether results of testing will change management re: long-term anticoagulation or for family knowledge
- Controversial, as rarely changes management but may explain why thrombosis provoked by nonsurgical major transient risk factor or pregnancy/OCP/HRT
- In Pts with no thrombosis history but have FHx of strong thrombophilia, consider testing for that thrombophilia. If ⊕, consider short-term ppx during high-risk situations.

Treatment

- Asx w/ inherited risk factor: consider prophylactic anticoag. if develops acquired risk factor
- Thrombosis w/ inherited risk factor: see “Venous Thromboembolism”
- Ante/postpartum Pts should receive prophylaxis for VTE when previous hx of VTE or if they have 2 inherited thrombophilias and no hx of VTE. Postpartum w/ AT3, protein C or S defic., and FHx of VTE should receive thromboprophylaxis (*Blood Adv* 2018;2:3317).

Antiphospholipid syndrome (APS) (*NEJM* 2018;398:2010)

- Revised Sapporo criteria: ≥1 clinical (thrombotic or obstetric) & ≥1 laboratory criteria. Newer ACR/EULAR criteria are more granular but less sensitive.
- Thrombosis: macrovascular venous or arterial thrombosis (including CVA)
- Obstetric: 3 spont. abortions before 10 wk or ≥1 fetal loss after 10 wk or premature birth before 34 wk due to preeclampsia or placental insufficiency with severe features
- Laboratory: ⊕ lupus anticoagulant (LA), or ⊕ moderate–high titer anticardiolipin (ACL), or ⊕ β_2-glycoprotein-I (β_2-GP-I) Ab, same Ab on ≥2 occasions, at least 12 wk apart. Values above 40 U and IgG are more significant than low-titer or isolated IgM. Anticardiolipin/β_2-GP-I: ELISA assays; okay on a/c; transient elevation w/ inflammation. LA may have false positive/negative if Pt on anticoagulation.
- Microvascular APS: involves small vessels w/ DAH, livedo reticularis, aPL nephropathy, cardiac injury. Other manifestations: cardiac valve thickening/vegetation, ↓ plt.
- Etiologies: primary (idiopathic) or secondary due to **autoimmune syndromes** (eg, SLE), **malignancy**, **infections**, drug reactions
- Treatment: UFH/LMWH → warfarin (lifelong for most Pts)
  - Warfarin preferred over DOACs in triple positive (⊕ ACL, LA, & β_2-GP) (*Blood* 2018;132:1365)
  - Initial *venous thrombosis:* warfarin INR 2–3, ? DOAC if not triple ⊕
  - Initial *arterial thrombosis:* warfarin INR 2–3 ± ASA 81 mg/d
  - *Recurrent thrombosis:* DOAC → warfarin, intensify INR goal, add ASA, LMWH/fonda
  - *Microvascular APS*: immunomodulatory approach varies

Catastrophic APS

- ≥3 organ systems in <1 wk w/ ⊕ APLA & tissue microthrombi; 44% mortality (*Arth Rheum* 2006;54:2568). If no macrovascular thrombosis in an affected organ system, consider microvascular injury with alternative imaging and biopsy.
- Rx: If acutely ill, do not wait for biopsy and labs. Prompt triple Rx w/ steroids, anticoagulation (heparin up front, transition to warfarin), and plasma exchange/IVIg. Consider rituximab and complement inhibition (eculizumab).

DISORDERS OF LEUKOCYTES

Neutrophilia (>7500–10,000/μL)	
Infection	Usually bacterial; ± toxic granulations, Döhle bodies
Inflammation	Burn, tissue necrosis, MI, PE, collagen vascular disease
Drugs and toxins	Corticosteroids, β-agonists, lithium, G-CSF; cigarette smoking
Stress	Release of endogenous glucocorticoids and catecholamines
Marrow stimulation	Hemolytic anemia, immune thrombocytopenia
Asplenia	Surgical, acquired (sickle cell), congenital (dextrocardia)
Neoplasm	Can be 1° (MPN) or paraneoplastic (eg, carcinomas of lung, GI)
Leukemoid reaction	>50,000/μL + left shift, not due to leukemia; unlike CML, ↑ LAP

Neutropenia (<1500/μL)	
Congenital	Duffy-null, myelokathexis, Shwachman–Diamond, Chédiak–Higashi, retic dysgen., WHIM, cyclic neutropenia, monoMAC syndrome (↓ monos, NKs)
Infection	Viral (CMV, EBV, HIV); bacterial (*Brucella*, *Rickettsia*, TB); malaria
Nutritional	Vitamin B12 or copper deficiency
Drugs and toxins	Chemotherapeutics, clozapine, methimazole, TMP–SMX, NSAIDs, sulfasalazine, phenytoin (*Am J Hem* 2009;84:428), alcohol
Neoplasm	MDS, leukemia (AML, ALL, hairy cell, LGL, others)

Monocytosis (>500/μL)	
Infection	Usually TB, SBE, *Listeria*, *Brucella*, *Rickettsia*, fungi, parasites, syphilis
Inflammation	IBD, sarcoidosis, collagen vascular diseases
Stress	MI, splenectomy, exercise (*Cytokine* 2013;61:364)
Neoplasm	Hodgkin lymphoma, leukemias, MPNs, carcinomas

Eosinophilia (>500/μL)	
Infection	Usually parasitic (helminths)
Allergic	Drugs; asthma, hay fever, eczema; ABPA

Collagen vasc dis.	RA, EGPA (Churg–Strauss), eosinophilic fasciitis, PAN
Endocrine	Adrenal insufficiency
Neoplasm	HL, CML, mycosis fungoides, carcinomas, systemic mastocytosis
Atheroembolic dis.	Cholesterol emboli syndrome
1° Hypereosinophilic syndrome	Multiorgan involvement incl. heart & CNS, a/w FIP1L1–PDGFRA fusion (*NEJM* 2003;348:1201); often steroid resistant

Basophilia (>200/µL)	
Neoplasm	MPN, CML, AML, Hodgkin lymph.
Infection	TB, smallpox, parasites
Alteration in BM or reticuloendothelial compartment	Hemolytic anemia, splenectomy
Inflammation or allergy	IBD, chronic airway inflammation

Lymphocytosis (>4000–5000/µL)	
Infection	Usually viral; “atypical lymphocytes” with mononucleosis syndromes Other: pertussis, toxoplasmosis
Hypersensitivity	Drug-induced, serum sickness
Autoimmune	Rheumatoid arthritis (large granular lymphocytes), malignant thymoma
Neoplasm	Leukemia (eg, CLL, hairy cell, LGL), lymphoma (eg, mantle cell, folic.)

Lymphadenopathy	
Viral	HIV, EBV, CMV, HSV, VZV, hepatitis, measles, rubella
Bacterial	Generalized (brucellosis, leptospirosis, TB, atypical mycobacteria, syphilis) Localized (streptococci, staphylococci, cat-scratch disease, tularemia)
Fungal/parasitic	Histo, coccidio, paracoccidioidomycosis, toxoplasmosis
Immunologic	Collagen vascular disease, drugs (eg, phenytoin), serum sickness, histiocytosis X, Castleman’s and Kawasaki disease
Neoplasm	Lymphoma, leukemia, amyloidosis, metastatic carcinoma
Other	Sarcoidosis; lipid storage diseases
Factors that favor biopsy	Pt >40 y, >2 cm, location (supraclavicular always abnl), duration >1 mo Consistency (hard *vs.* rubbery *vs.* soft) & tenderness are not reliable Excisional biopsy preferred over fine-needle aspiration (FNA)

TRANSFUSION MEDICINE

Blood Products and Indications (*Lancet* 2013;381:1845; *JAMA* 2023;330:1892)	
Packed red blood cells (PRBCs)	For acute blood loss or to ↑ O_2-carrying capacity if end organ ischemia. 1 U PRBC → ↑ Hb by ~1 g/dL. Hb goal >7 g/dL adequate for UGIB & critically ill (*NEJM* 2013;368:11 &

	2014;371:1381). Mixed data for ≥8 vs. ≥10 in acute MI (*JAMA* 2021;325:552; *NEJM* 2023;389:2446).
Platelets (plts) (*Annals Int Med* 2015;162:205)	For plts <10k due to chemo/abx. If <20k or if <50k w/ active bleed. Variable preprocedure (consider for CVC if <50k [*NEJM* 2023;388:1956]).100k for neurosurgery. 1 U → ↑ plt ~30–60k. Single donor plt apheresis ↓ alloimmunization. *Contraindic:* TTP/HUS, HELLP, HIT *Refractory* if ↑ <5k 30–60′ post-plts. Suggests consumption such as ITP, DIC, or alloimmunization → trial ABO-matched plts & give more. If still refractory ✓ panel reactive Abs to assess utility of HLA-matched plts.
Fresh frozen plasma (FFP)	Contains all coagulation factors. For bleeding due to defic. of multiple coag factors (eg, DIC, TTP/HUS, liver disease, dilution). Nb, reverse warfarin w/ Kcentra = 4 factor PCC (*JACC* 2020;76:594).
Cryoprecipitate	Enriched for fibrinogen, vWF, VIII, and XIII. 1st line for fibrinogen <100 mg/dL. For bleeding in vWD factor XIII deficiency, use if other products not available.
Irradiated	Prevents donor T-cell engraftment and risk of transfusion-assoc. GVHD (HSCT, heme malignancy, congenital immunodeficiency).
CMV-negative	From CMV-negative donors. For CMV-seronegative pregnant women, transplant candidates/recipients, SCID, AIDS Pts.
Leuko-reduced	WBCs cause HLA alloimmunization & fever (cytokines) and carry CMV. For chronically transfused Pts, potential Tx recip., h/o febrile nonhemolytic transfusion rxn, cases in which CMV-neg products desired but unavailable.
IV immune globulin (IVIg)	Polyvalent IgG from >1000 donors. For postexposure prophylaxis (eg, HAV), certain autoimmune disorders (eg, ITP, Guillain–Barré, MG, CIDP), congenital or acquired hypogammaglobulinemia (CVID, CLL).
Therapeutic apheresis	Removes plasma large molec wt subst. (eg, cryoglobulinemia, Goodpasture's, Guillain–Barré, hyperviscosity syndrome), or cells (eg, leukemia w/ hyperleukocytosis, sx thrombocytosis) from plasma. TTP: replace ADAMTS13. RBC exchange for SCD acute chest or stroke.
Massive transfusion	Large-vol. PRBC → ↓ Ca, ↑ K, ↓ plt, ↑ coags; initial ratio of 1 PRBC: 1 plt:1 FFP accepted but controversial, follow labs (*JAMA Surg* 2017;152:574)

Transfusion Complications (*NEJM* 2017;377:1261)

Noninfectious	**Risk (per unit)**	**Infectious**	**Risk (per unit)**
Febrile	1:100	CMV	Common
Allergic	1:100	Hepatitis B	1:220,000
Delayed hemolytic	1:50–75,000	Hepatitis C	1:1,600,000
Acute hemolytic	1:200,000	HIV	1:1,800,000
Febr. non-hemolytic	1:200	Bacteria (PRBCs)	1:500,000
TRALI	1:5000	Bacteria (platelets)	1:12,000

Transfusion reactions

- Reason why blood products (unless massive tfn) run 1 at a time. For all rxns (except minor allergic): **stop txfusion;** send remaining blood product + fresh blood draw to blood bank.
- **Acute hemolytic:** fever, HoTN, flank pain, AKI w/in 24 h. Due to ABO incompatibility → preformed Abs vs. donor RBCs. Rx: IVF, ↑ UOP w/ diuretics, mannitol, or dopamine.
- **Delayed hemolytic:** generally less severe than acute hemolytic; 5–7 d after transfusion, but can be severe → hyperhemolysis. Due to undetected allo-Abs vs. minor antigens → anamnestic

response. Rx usually not required; dx important for future transfusion.

- **Febrile nonhemolytic:** fever, rigors 0–6 h posttransfusion. Due to Abs vs. donor WBCs and cytokines in blood product. Rx: acetaminophen ± meperidine; r/o infection, hemolysis.
- **Allergic:** urticaria; rarely, **anaphylaxis** due to rxn to txfused proteins, especially in IgA- deficient Pts w/ anti-IgA Abs (use washed products). Rx: urticaria → diphenhydramine; anaphylaxis → epinephrine ± steroids. Washed products ↓ rxns in chronic txfusions.
- **Transfusion-associated circulatory overload** (TACO): ↑ volume → pulm. edema, ↑ **BP**. Rx: slow transfusion rate, diuretics, O_2, ± nitrates, ± positive pressure ventilation.
- Tfn-related acute lung injury (TRALI): non-cardiogenic pulm. edema due to donor allo-Abs from multiparous ♀ plasma binding WBCs. No longer seen in U.S. as plasma only from ♂.

MYELOID NEOPLASMS

Overview (*Leukemia* 2022;36:1703)

- Categories based on clinical features, morphology, immunophenotyping, and genetics

WHO 2022 Classification of Myeloid Neoplasms & Acute Leukemia	
Acute myeloid leukemia	Clonal myeloid stem cell (SC) disorder w/ ≥20% blasts *or* defining genetic abnormalities
Myelodysplastic syndromes	Dysplastic clonal myeloid SC disorder → cytopenias; <20% blasts, risk of leukemic transformation
Myeloproliferative neoplasms	Nondysplastic multipotent myeloid SC clonal expansion (eg, ET, PV, MF)
MDS/MPN neoplasms	Features of MDS & MPN (eg, CMML, atypical CML)
Mastocytosis	Clonal mast cell disorder, assoc w/ *KIT* mutations
Myeloid neoplasms w/ germ line predisposition	MDS, MDS/MPN, acute leukemias in background of predisposing germline mutations (eg, *DDX41*)
Myeloid precursor lesions	Clonal hematopoiesis of indeterminate significance (CHIP); clonal cytopenia of undetermined significance (CCUS)

Myelodysplastic syndromes (MDS) overview (*JAMA* 2022;328:872)

- Acquired clonal stem cell disorder → ineffective hematopoiesis → **cytopenias**, **dysmorphic blood cells & precursors (<20% BM blasts)**, variable risk of **leukemic transformation**
- Epidemiology: 4 cases/100,000 people; median age ~70 y; male predominance (1.8×)
- **Idiopathic** or 2° to chemo w/ **alkylating agents;** ↑ risk w/ radiation, benzene
- Clinical manifestations: **anemia** (85%) w/ ↑ MCV and ↑ RDW, neutropenia (50%), thrombocytopenia (40–65%)
- Diagnosis: dysplasia (usually multilineage) in peripheral smear (oval macrocytes, **pseudo-Pelger–Huët anomaly**) and bone marrow (≥10% dysplasia ± RS or >5% blasts)
- Both **cytogenetic** [eg, del(5q), mono 7, del(7q), trisomy 8, del(20q)] and **molecular** abnl (*TP53*, *GATA2, RUNX1, TET2, ZRSR2, STAGE2, ASXL1*) carry prognostic significance
- Prior to dx MDS: exclude AML (≥20% blasts or cytogenetics such as t(15;17), t(8;21), inv16, t(16;16), or *MLL* rearrangement), and CMML (monos >1 × 10^9/L and >10% on diff); r/o 2° BM Δs (defic. of B_{12}, folate, copper); viral infxn (eg, HIV); EtOH; lead, arsenic

WHO 2022 Classification Systems for MDS (*Leukemia* 2022;36:1703)		
Classification	**Features**	**Blast Percentage**
MDS-5q	Del(5q); low blasts	<5% in BM; <2% in PB
MDS-SF3B1	SF3B1 mutation; low blasts	<5% in BM; <2% in PB
MDS-biTP53	Biallelic TP53 mutant	<20% in BM and PB
MDS, NOS	Dysplasia	<20% in BM
MDS-IB1	Mildly increased blasts	5–9% in BM or 2–4% in PB
MDS-IB2	Moderately increased blasts	10-19% in BM *or* 2-19% in PB *or* Auer rods
MDS w/ fibrosis	Increased reticulin staining	5–19% in BM *or* 2–19% in PB

BM, bone marrow; PB, peripheral blood

- Prognosis: risk stratification performed per IPSS-M scoring system (https://mds-risk-model.com/) that factors in age, BM blast %, cytopenias, cytogenetics, and individual mutations (*NEJM Evid* 2022;1:EVIDoa2200008)
- Rx intensity based on IPSS-M, age, performance status (PS), transplant eligibility
- Poor PS, any risk
  - supportive: transfusions, G-CSF, erythropoietin-stimulating agents (ESA), TPO-mimetics
- Very low/low risk (IPSS-M)
  - ESA if epo <500; TPO-mimetic agents; transfusions (monitor for iron overload using ferritin in transfusion-dependent Pts)
  - lenalidomide (espec. for MDS-5q); luspatercept (neutralizes TGF-β; particularly effective in SF3B1 mutant disease, *Lancet Hem* 2024;11:646)
  - imetelstat (telomerase inhibitor) in ESA-refractory/ineligible patients (*Lancet* 2024;403:249)
- Interm/high risk (IPSS-M)
  - **DNA methyltransferase inhibitor** azacitidine or decitabine or oral decitabine/cedazuridine; addition of venetoclax being evaluated (*Lancet* 2024;11:186)
  - **allogeneic HSCT** if medically fit (*JCO* 2021;39:3328)

MYELOPROLIFERATIVE NEOPLASMS (MPN)

General (*NEJM* 2017;376:2168)

- Results from clonal expansion of multipotent hematopoietic stem cell
- Categories of MPN: **polycythemia vera** (PV); **essential thrombocythemia** (ET); **primary myelofibrosis** (PMF); chronic myelogenous leukemia (CML; *BCR-ABL1* ⊕); atypical CML (aCML); chronic neutrophilic leukemia (CNL); systemic mastocytosis (SM); hypereosinophilic syndrome (HES); MPN-NOS/unclassifiable
- MDS/MPN neoplasms: proliferative and dysplastic features
- Mutations useful as clonal markers & dx tools:
  - Gain of fxn mutations in ***JAK2*** V617F (Janus kinase) frequently present (PV ~95%, ET ~50%, PMF ~50%)
  - ***BCR-ABL1*** fusion in **all** cases of CML; ***SETBP1*** in aCML
  - ***CALR*** exon 9 mutation, type I and II (most MPNs w/o *JAK2* or *MPL* mutation, including ~25% of ET, ~35% of myelofibrosis Pts). Type I has better prognosis.
  - ***CSF3R*** mutation present in ~60% of CNL; ***KIT*** D816V in 95% of systemic mastocytosis
  - ***FIP1L1-PDGRFa*** *translocation present in ~15% of HES* (male predominant)

Polycythemia Vera (PV) (*JAMA* 2025;333:153)

Definition

- ↑ in RBC mass ± ↑ granulocytes and platelets in the absence of physiologic stimulus

Etiologies of erythrocytosis (absolute ↑ RBC)

- Acquired 1°: PV (usually *JAK2*+) or other MPN
- Germline 1°: Chuvash (VHL mutation), and HIF2a and EGLN mutations
- Secondary: **carboxyhemoglobinemia; hypoxia** (OSA, COPD); **inappropriate erythropoietin** (renal, hepatic malignancy); Cushing's syndrome
- Mimics: *relative* ↑ RBC (↓ plasma) due to dehydration; "stress" erythrocytosis (Gaisböck's syndrome)

Clinical manifestations (common between PV and ET)

- Symptoms (often termed "vasomotor")
  - **Hyperviscosity** (erythrocytosis): headache, dizziness, tinnitus, blurred vision
  - **Thrombosis** (erythrocytosis; JAK2+): ↑ **risk of DVT**, **MI**, **stroke**; transient visual disturbances (amaurosis, ocular migraine); Budd–Chiari syndrome; erythromelalgia = intense burning, pain, and erythema of extremities due to microvascular ischemia
  - **Bleeding** (abnormal platelet function): easy bruising, epistaxis, GI bleeding
  - ↑ histamine from basophils → **pruritus (aquagenic)**, peptic ulcers
  - ↑ uric acid (cell turnover) → gout
- Signs: **plethoric facies**, **splenomegaly**, hypertension, engorged retinal veins

Diagnostic evaluation

- Men: Hb >16.5 g/dL or Hct >49%, women: Hb >16 g/dL or Hct >48%
- ± ↑ WBC, platelets, basophils; ↑ uric acid, leukocyte alkaline phosphatase, vit. B_{12}
- Peripheral smear → no morphologic abnormalities
- ✓ Epo to rule out secondary causes of erythrocytosis; **if Epo ↓**, **PV more likely**.
  If Epo ↑, then ✓ SaO_2 or PaO_2, carboxyhemoglobin, BM exam.
- BM bx → hypercellularity for age, trilineage growth, pleomorphic mature megakaryocytes
- ***JAK2* V617F** mutation in ~95% of PV; other Pts typically harbor *JAK2* exon 12 mutations

Treatment for *JAK2*+ PV

- **Phlebotomy** to goal Hct <45% (goal is iron deficiency; avoid Fe repletion) (*NEJM* 2013;368:22)
- **Low-dose ASA** in all Pts (*NEJM* 2004;350:114)
- **Hydroxyurea** if high risk of thrombosis (age ≥60 *or* prior thrombosis) or if inadequate Hct by phlebotomy alone
- Ropeg (IFNα) preferred in younger Pts and during preg. (*NEJM Evid 2023;2:EVIDoa*2200335)
- Ruxolitinib (JAK1/2 inhibitor), Ropeg, and busulfan if refractory to or intolerant of hydroxyurea (*NEJM* 2015;372:426)
- Supportive: allopurinol (gout), H_2-blockers/antihistamines (pruritus)
- Rusfertide (hepcidin mimetic) under study (*NEJM* 2024;390:723)

Prognosis

- Median survival w/ Rx ~13.5 y (*Blood* 2014;124:2507); ↑ age, WBC, additional acquired somatic mutations → worse prognosis (*Haematol* 2013;160:251)
- Post-PV myelofibrosis (spent phase) occurs in 10–20% of cases, usually after 10 y
- Risk of transformation into acute leukemia (<2–5% lifetime)

Essential Thrombocythemia (ET) (*JAMA* 2025;333:701)

Definition

- Sustained ↑ in platelets (>450,000/μL) ± ↑ RBC and granulocytes

Etiologies of thrombocytosis

- 1° = ET or other MPN/MDS (5q-syndrome, SF3B1 mutation)
- 2° = **reactive thrombocytosis:** inflammation (RA, IBD, vasculitis), infection, trauma, acute bleed, **iron deficiency**, postsplenectomy, neoplasms (eg, Hodgkin lymphoma)
- Of patients with plt >1,000,000/μL, <1 in 6 will have ET

Clinical manifestations (also see "Polycythemia Vera")

- Thrombosis with erythromelalgia (risk of thrombosis highest in Pts with leukocytosis), bleeding (acquired vWD), pruritus; mild splenomegaly; migraine, TIA; early fetal loss

Diagnostic evaluation

- Peripheral smear: large hypogranular platelets
- BM bx: megakaryocytic hyperplasia; ⊖ Phil chr; rarely minor reticulin fibrosis; nl Fe; if atypical megakaryocytes or ↑ reticulin, consider pre-PMF (Rx same as ET, but ↑ risk MF)
- Mutations: ***JAK2* V617F** in ~50%; ***CALR*** in ~45%; ***MPL*** in 5–10%; triple negative <5%
- Patients should not meet WHO criteria for diagnosis of CML, PV, PMF, or MDS
- Check vWF in Pts w/ plt >1,000,000 and hold ASA (vide infra) if acquired vWD

Treatment of ET (*Blood Cancer J* 2015;5:e369)

Risk	Age	h/o Thrombosis	*JAK2*	ASA 81 mg qd	Cytoreduction
Very low	<60	N	⊖	Consider if CV risk factors	No
Low			⊕	⊕	No
Intermed	≥60	N	⊖	⊕	±
Very high	≥60	N	⊕	⊕ (hold if lab evid. of acquired vWD)	**Hydroxyurea**, IFNα if young or pregnant
	Any	Y	Any		

Prognosis

- Low-risk Pts have overall survival ≈ control population
- Risk of transformation into acute leukemia <2–3% lifetime; risk of progression to MF ~10%

Myelofibrosis

Definition

- Clonal myeloproliferation with reactive marrow fibrosis & extramedullary hematopoiesis

Etiologies of myelofibrosis

- 1° myelofibrosis (PMF): myeloproliferative neoplasm

- 2° myelofibrosis: post-PV/ET myelofibrosis, other hematologic (CML, AML, ALL, MDS) and solid cancers (breast, prostate), autoimmune (eg, SLE), toxin (benzene), radiation, granulomas (TB, fungal, sarcoid), deposition diseases (eg, Gaucher's)

Clinical manifestations (*BJH* 2012;158:453)

- Ineffective erythropoiesis → anemia; extramedullary hematopoiesis → **massive splenomegaly** (abdominal pain, early satiety) ± hepatomegaly
- Tumor bulk and ↑ cell turnover → fatigue, weight loss, fever, sweats

Diagnostic evaluation (*Blood* 2010;115:1703 & 2016;127:2391)

- Anemia with variable WBC and platelet counts
- Peripheral smear → "**leukoerythroblastic**" (**teardrop cells**, nucleated RBCs, immature WBCs); large abnormal platelets
- BM aspirate → "dry" tap; BM bx → **severe fibrosis**, replacement by reticulin & collagen
- ***JAK2* V617F** in 45–50%; ***CALR*** mut in 45–50%, ***MPL*** mut in 7–10%, triple neg in 1–2%
- No *BCR-ABL* translocation; Pts should not meet criteria for PV or MDS
- MIPSS70+v2.0 score for prognosis: calculated using clinical factors (WBC >25k, Hgb <10, plt <100, peripheral blasts ≥2%, constitutional sx); mutational status and cytogenetics

Treatment (*Am J Hematol* 2021;96:145)

- In absence of adverse prognostic factors (eg, anemia or sx) → no treatment
- Allogeneic HSCT only potential cure → consider in young Pts w/ high-risk disease
- Supportive care: **transfusions;** ESA if Epo <500 (risk ↑ splenomegaly)
- **JAK inhibitor**: ruxolitinib (JAK1/2) ↓ sx, ↓ splenomegaly, ↑ survival; preferred (*NEJM* 2012;366:787 & 799); other options include fedratinib (JAK2; check thiamine [risk of Wenicke's]; *JAMA Onc* 2015;1:643); pacritinib (JAK2/FLT3/ACVR1 inhib; use for plt <50k) (*JAMA Onc* 2018;4:652) & momelotinib (JAK and ACVR1 inhib; use w/ plt >50 + anemia) (*Lancet* 2023;401:269)
- Median survival ~6 y (*JCO* 2012;30:2981); transformation into AML occurs at a rate of ~8%/y

LEUKEMIA

Acute Leukemia

Definition

- Clonal proliferation of hematopoietic stem cells w/ failed differentiation into mature elements → ↑ blasts in BM and occasionally periphery → ↓ RBCs, platelets, and neutrophils

Epidemiology and risk factors

- Acute myeloid (AML): ~20k cases/y in U.S.; median age 68 y
- Acute lymphoblastic (ALL): ~6k cases/y in U.S.; median age 15 y but 2nd peak at 50 y
- Risk factors: **radiation**, **chemo** (alkylating agents, topo II inhib), benzene, smoking ? rising from acquired somatic mutations and clonal hematopoiesis (*NEJM* 2014;371:2477)
- Secondary to acquired hematopoietic dis.: MDS, MPN (esp. CML), aplastic anemia, PNH
- Inherited: Down's, Klinefelter's, Fanconi's anemia, Bloom synd., ataxia telangiectasia, germline mut. in *TP53* (Li–Fraumeni syndrome)*, DDX41, RUNX1*, *CEBPa, & GATA2*

Clinical manifestations

- Cytopenias → **fatigue** (anemia), **infection** (neutropenia), **bleeding** (thrombocytopenia)
- **Leukostasis** (more in AML): blast >50k, ↓ SaO_2, HA, blurry vision, confusion, TIA/CVA
- **Tumor lysis syndrome** (TLS) from rapid turnover of cells
- **Disseminated intravascular coagulation** (**DIC**; especially with APL)
- Other: leukemic infiltration of skin, gingiva (esp. with monocytic subtypes); chloroma (myeloid sarcoma): extramedullary tumor of leukemic cells, any location; anterior mediastinal mass and SVC syndrome (T-ALL/LBL); hepatosplenomegaly (ALL and monocytic leukemias); leukemic pneumopathy; CNS (~10% of ALL; also in monocytic > myeloid): cranial neuropathies, HA

Diagnostic evaluation (*Blood* 2009;114:937)

- **Peripheral smear:** thrombocytopenia, **blasts** (seen in >95%; ⊕ Auer rods only in AML)
- **Bone marrow:** >20% blasts or disease defining mutation w/ increased blasts; test for cytogenetics and flow cytometry for immunophenotype (AML/ALL)
- **Cytogenetic anomalies**: eg, in AML, t(15;17), t(8;21), inv(16) or t(16;16), complex; in ALL, Ph-chromosome [t(9;22)], hyper or hypodiploid, complex
- Molecular mutations in AML: esp *FLT3* (ITD and TKD), *TP53, NPM1;* ALL*: BCR-ABL1*
- Evaluate for complications: TLS (↑ uric acid, ↑ LDH, ↑ K, ↑ PO_4, ↓ Ca), DIC (↑ PT & PTT, ↓ fibrinogen, ↑ D-dimer), check for G6PD (prior to giving rasburicase)
- Lumbar puncture with **intrathecal chemotherapy** to avoid seeding CSF w/ circulating blasts) for all Pts w/ ALL (CNS is sanctuary site) and for Pts w/ AML w/ CNS sx
- Transthoracic echocardiogram before use of anthracyclines
- **HLA typing** of Pt, siblings > parents/children for potential allogeneic HSCT candidates
- Check β-hCG levels prior to chemo; offer fertility preservation in younger Pts
- Consider ovarian suppression (leuprolide) to limit menses while thrombocytopenic

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Acute Myeloid Leukemia (AML)

Classification (WHO; *Blood* 2016;127:2391)

- Features that confirm myeloid lineage and subclassify AML to guide treatment: morphology: **blasts**, ⊕ **granules**, ± **Auer rods** (eosinophilic needle-like inclusions, specific for myeloid lineage)
- Immunophenotype: precursor: CD34, CD45, HLA-DR; myeloid: CD13, CD33, CD117; monocytic: CD11b, CD64, CD14, CD15
- Histochem: myeloperoxidase (MPO; myeloid), and lysozyme (monocytic)
- Prognosis: *age*, prior *antecedent MPN/MDS*, and *genetics* (cytogenetics + molecular mutation status) are key independent risk factors of poor prognosis

ELN 2022 Genetic Risk Classification (Adapted with permission from *Blood* 2022;140(12):1345–1377.)

Risk Category	Genetic Abnormality
Favorable	t(8;21): *RUNX1-RUNX1T1*; inv(16): *CBFB-MYH1*; mutated *NPM1 w/o FLT3-ITD* bZIP in-frame mutated *CEBPA*
Intermediate	mutated *NPM1* w/ *FLT3-ITD*; wild-type *NPM1* w/ *FLT3-ITD (w/out adverse-risk genetic lesions);* t(9;11): *MLL-MLLT3*; cytogenetic abnl not classified as favorable or adverse
Adverse	−5 or del(5q); −7; −17/abn(17p); t(6;9): *DEK-NUP214*; t(9;22) *BCR-ABL1*; inv(3): *GATA2-MECOM*; wild-type *NPM1* & *FLT-ITD*; t(v;11q23.3):KMT2a-rearranged; t(8;16):KAT6A-CREBBP; inv(3q26.2;v):MECOM(EVI1)-rearranged; complex or monosomal karyotype; mutated *TP53, RUNX1, ASXL1*, and others

Upfront treatment (*Lancet* 2023;401:2073)

- **Cytoreduction:** start hydroxyurea when >50k blasts to ↓ risk of TLS and DIC w/ induction
- **Induction chemo:** regimen determined by fitness and genetic risk
- **Regimens for *fit*** (generally age <75 y): "7+3" = 7 d infusion cytarabine (Ara-C) + 3 d bolus anthracycline (daunorubicin or idarubicin); FLAG (fludarabine, cytarabine, G-CSF) plus idarubicin, liposomal daunorubicin plus cytarabine (CPX-351; Vyxeos), especially in secondary or therapy-related AML
  - *FLT3*-ITD/TKD mutation: 7+3+midostaurin (FLT3-ITD/TKD inhib; *NEJM* 2017;377:454) or 7+3+quizartinib (FLT3-ITD inhib only; *Lancet* 2023;401:1571)
  - Core-binding factor ⊕: t(8;21) or inv(16): 7+3 ± gemtuzumab ozogamicin (mAb targ. CD33)
  - 2° AML or w/ MDS-related changes: CPX-351; Vyxeos (*JCO* 2018;36:2684)
- **Regimens for *unfit*** (age ≥75 y or <75 y w/ ECOG ≥3 or severe comorbidities)
  - Hypomethylating agents (HMA) ± venetoclax (Bcl2 inhibitor, ↑ TLS) (*NEJM* 2020;383:617)
  - *IDH1/2* mutation: ivosidenib or enasidenib ± azacitidine, or single-agent HMA esp in TP53-mutated AML
- Obtain BM bx 14–21 days after start of induction chemo to assess response
- **Measurable residual disease** (MRD): malignant cells present after treatment under morphologic detection threshold; can detect using flow cytometry or sequencing assays; MRD highly prognostic of outcomes (*Blood* 2018;131:1275)

Consolidation therapy

- If *complete remission* (CR) = ANC >10^3, plt >100, no RBC Rx, <5% BM blasts; **CR ≠ cure**
- Favorable risk: high-dose cytarabine (HiDAC); intermediate/poor risk: Allo-HSCT
- Consider oral maintenance azacitidine if cannot complete curative intent Rx (*NEJM* 2020;383:2526)

Refractory/relapsed disease

- *Repeating mutation analysis* key b/c clonal evolution common and may affect Rx
- *FLT3*-ITD/TKD mutation: gilteritinib (potent FLT3 inhibitor)
- *IDH1/2* mutation: ivosidenib (*IDH1* inhib): enasidenib (*IDH2* inhib)
- Chemo: MEC (mitoxantrone, etoposide, Ara-C); FLAG-Ida (fludarabine, Ara-C, G-CSF, & idarubicin); HMA+venetoclax (if not already attempted)
- Always consider clinical trials

Prognosis

- CR achieved in 70–80% of Pts <60 y and in 40–50% of Pts >60 y
- Overall survival variable, depends on prognostic factors: ranges from <10% of older Pts w/ poor-risk tumor genetics to >65% of younger Pts w/ favorable prognostic factors

Acute promyelocytic leukemia (APL) (*Blood* 2009;113:1875)

- Rare, ~8% of AML in U.S.; >90% cure rates
- Atypical promyelocytes (large, granular cells; bilobed nuclei) in blood and bone marrow
- Defined by translocation of retinoic acid receptor: **t(15;17); *PML-RARA*** (>95% of cases)
- **Medical emergency** with **DIC** and **bleeding** common
- Remarkable responses to **all-*trans*-retinoic acid (ATRA)** & **arsenic trioxide (ATO)** which induce differentiation of leukemic blasts. ***∴ early initiation of ATRA if APL suspected.***
- Non-high-risk APL: ATRA + ATO (induction + 4 cycles consolidation) → CR ~100%; event-free survival 97% and overall survival 99% at 2 y (*NEJM* 2013;362:111)
- High-risk APL: WBC >10k at diagnosis. No clear consensus. In general, chemo (anthracycline or gemtuzumab ozogamicin) added to ATRA + ATO induction and consolidation.
- Differentiation syndrome (ATRA): ~25% of Pts; fever, pulm. infiltrates, SOB, edema, HoTN, AKI; tx w/ dexamethasone 10 mg bid, supportive care (eg, diuresis) (*Blood* 2008;113:775)

Acute Lymphoblastic Leukemia (ALL; *Lancet* 2020;395:1146

Classification

- Lymphoblastic neoplasms may present as acute leukemia (ALL) w/ >**25% BM blasts** or as lymphoblastic lymphoma (LBL, more common in T-cell) w/ mass lesion w/ <25% BM blast
- Morphology: **no granules** (granules seen in myeloid lineage)
- Cytochemistry: ⊕ terminal deoxynucleotidyl transferase (TdT) in 95% of ALL, MPO ⊖
- Immunophenotype: **precursor**: CD34, TdT; **B cell**: CD19; variable CD10, CD22, CD79a; **T cell**: CD1a, CD2, cytoplasmic CD3, CD5, CD7

Treatment

- **Induction chemo**
  - Ph ⊕ t(9;22) (seen in ~25% of B-ALL): TKI + steroids + blinatumomab (*JCO* 2024;42:881)
  - Ph ⊖: adolescents & young adults (<40 y): pedi-inspired regimen typically w/ PEG-asparaginase. Adults (40–60 y): multiagent chemo incl. anthracycline, vincristine, steroids, cyclophosphamide. Older (>60 y): reduced-intensity chemo.
  - Ph-like: genetic profile similar to Ph ⊕, assoc. w/ poor outcomes, treated like Ph ⊖
  - Goal is MRD ⊖ (<0.0001) remission
  - Addition of blinatumomab (enables T cells to recog malig B cells) for MRD ⊖ & ⊕ ALL
- **CNS prophylaxis:** intrathecal MTX ± cytarabine ± cranial irradiation
- **Post-remission therapy** (choice depends on risk of recurrence)
  - Average risk: consolidation/intensification chemo (~7 mo) → maintenance (~2–3 y)
  - High risk: high-dose chemo w/ allo-HSCT considered for Pts in CR1. High-risk disease includes: Ph ⊕; Ph-like; MLL translocation t(4;11); complex karyotype; hypodiploid (<44 chromosomes); early T-cell phenotype (ETP; lacks CD1a, CD8, CD5^{weak}, myeloid markers). Ph⊕ MRD⊖ benefit from consolidation blinatumomab (*NEJM* 2024;391:320).
- **Relapse/refractory:** salvage therapy (*below*), then allogeneic HSCT if able
  - *B cell:* blinatumomab (*NEJM* 2017;376:836), inotuzumab (CD22 Ab-drug conjugate; *NEJM* 2016;375:740); CD19 **CAR-T** (tisagenlecleucel, brexucabtagene autoleucel [*NEJM* 2018;378:449; *Lancet* 2021;398:491]; obecabtagene autoleucel [*NEJM* 2024;391:2219]), TKI + chemo/steroids
  - *T cell:* nelarabine ± cyclophosphamide and etoposide (*BJH* 2016;150:245)
  - *Both B & T cell:* chemo including high-dose cytarabine regimens; clofarabine

Chronic Myelogenous Leukemia (CML; *JAMA* 2025;333:1618)

Definition (*Blood* 2009;114:937)

- **Myeloproliferative neoplasm** with clonal overproduction of hematopoietic myeloid stem cells that can differentiate
- **Philadelphia chromosome** (Ph) = t(9;22) → ***BCR-ABL1*** fusion → ↑ Abl kinase activity
  BCR-ABL1 required for diagnosis (make via karyotyping or FISH; PCR)

Epidemiology and risk factors

- ~6600 new cases/y in U.S.; median age ~64 at presentation; ~15% of adult leukemias
- ↑ risk with irradiation; no clear relation to cytotoxic drugs

Disease classification & manifestations (*Blood* 2016;127:2391)

- **Chronic phase (CP):** <10% blasts (peripheral or bone marrow). Risk stratification based on Sokal (*Blood* 1984;63:789) or Euro scores (*J Clin Pathol* 2001;54:491).
- **Accelerated phase (AP):** 10–19% blasts, ≥20% basos, plts <100k
- **Blastic phase (BP):** ≥20% blasts (peripheral or marrow) and/or extramedullary leukemia

- Most Pts asx or may have mild constitutional s/s related to splenomegaly
- Worsening constitutional sx, bone pain, rapid ↑ in spleen size herald disease progression

Diagnostic evaluation

- **Peripheral smear: leukocytosis**, left-shifted with *all stages of myeloid maturation*; thrombocytosis, **basophilia**
- **Bone marrow w/ karyotype:** hypercellular, ↑myeloid:erythroid ratio, micromegakaryocytes

Treatment (*Lancet* 2015;385:1447; *Hematol Oncol Clin North Am* 2017;31:577)

- **Tyrosine kinase inhibitors (TKI)** inhibit abl kinase activity
  - 1st gen: imatinib; 2nd gen: nilotinib, dasatinib, bosutinib; 3rd gen: ponatinib; high potency, ↑ CV toxicity (vide infra). All are ATP-mimetic agents.
  - Asciminib is allosteric inhibitor (*NEJM* 2024;391:885); different tox profile than rest
  - All agents approved for 1st line Rx. Only ponatinib & asciminib effective on T315I mutation (*NEJM* 2012;367:2075; *Blood* 2021;138:2031).
  - Resistance: due to ↑ *BCR-ABL1* expression, often 2/2 *ABL* kinase mutation or amplification
  - Side effects: N/V, diarrhea, muscle cramps, cytopenias, ↓ PO_4, ↑ QT, rarely CHF
    - dasatinib: pericardial & pleural effusions and pulmonary HTN
    - nilotinib: ↑ bili & lipase, CV toxicity (HTN, arrhythmias)
    - ponatinib: pancreatitis and arterial vascular events (cerebral, cardiac, & PAD)
    - bosutinib: diarrhea very common
    - asciminib: arthralgia, ↑ LFT & lipase w/o risk of pancreatitis
- Consider allogeneic HSCT for AP and BP
- CML in pregnancy: hydroxyurea & TKIs contraind. IFN or leukapheresis (if nec.).
- With adequate treatment can achieve near-normal life expectancy (*Cells* 2023;12:1703)
- **TKI discontinuation**: consider if complete molecular response (>4.5 log reduction in *BCR-ABL1* transcript) for >2 y. Up to 50% of Pts remain off TKI at 2 y (ie, no molecular recurrence). Success proportional to duration of CMR and risk score at presentation (*JCO* 2024;42:1875).

LYMPHOMA AND CLL

Definition

- Malignant disorder of lymphoid cells that reside predominantly in lymphoid tissues
- Generally characterized as **Hodgkin lymphoma** (HL) or **non-Hodgkin lymphoma** (NHL)

Clinical manifestations

- Lymphadenopathy (usually nontender)
  - superficial (usually **cervical/supraclavic.**) ± mediastinal (esp. HL; risk for SVC syndrome)
  - **nodal** disease can have **anatomic OR noncontiguous spread** to adjacent nodes and structures, symptoms reflect involved sites (abdominal fullness, bone pain)
- Constitutional ("B") symptoms: **fever** (>38°; Pel–Ebstein fever in HL), drenching **sweats**, ↓ **weight** (>10% in 6 mo)

Diagnostic and staging evaluation

- Physical exam: lymph nodes, liver/spleen size, Waldeyer's ring, testes (~1% of NHL), skin
- Pathology: **excisional (preferred) or core lymph node bx** (*not FNA* b/c need surrounding architecture; avoid steroids prior to bx if possible) with immunophenotyping and cytogenetics

(**Reed–Sternberg** (RS) **cells in HL**); CLL by peripheral flow in patients w/ peripheral disease; consider BM bx if cytopenias; LP if CNS involvement clinically suspected
- Lab: CBC, BUN/Cr, LFTs, ESR, LDH, UA, Ca, alb; ✓ HBV & HCV (and must ✓ HBsAg & anti-HBc if planning rituximab Rx due to risk of HBV reactivation); HIV; G6PD for TLS Rx
- Imaging: **PET-CT** necessary in all lymphomas to assess disease burden/staging and guide biopsy/therapy. Head CT/MRI *only* if neurologic symptoms.

Ann Arbor Staging with Lugano Modifications (*JCO* 2013;54:8800)	
Stage	**Features**
I	Single lymph node (LN) region
II	≥2 LN regions on the same side of the diaphragm
III	LN regions on both sides of the diaphragm
IV	Disseminated involvement of one or more extralymphatic organs
Modifiers: A (only HL) = no symptoms; B (only HL) = fever, night sweats, or weight loss; E = single contiguous extranodal site	

Hodgkin Lymphoma (Hl) (*Am J Hematol* 2018;93:704; *Lancet* 2021;398:1518)

Epidemiology and risk factors

- ~9000 cases/y; bimodal distribution (15–35 & >50 y); ↑ ♂; role of EBV in subsets of HL, esp. immunocompromised patients (eg, HIV)

Pathology

- Affected nodes show RS cells (<1%) in background of nonneoplastic inflammatory cells
- Classic RS cells: bilobed nucleus & prominent nucleoli with surrounding clear space ("owl's eyes"). RS cells are **clonal B cells:** CD15+, CD30+, CD20– (rarely +).

WHO Histologic Classification of Classical HL		
Nodular sclerosis	60–80%	Collagen bands; frequent mediastinal LAN; young adults; female predominance; usually stage I or II at dx
Mixed cellularity	15–30%	Pleomorphic; older age; male predominance; ≥50% stage III or IV at presentation; intermediate prognosis
Lymphocyte rich	5%	Abundant normal-appearing lymphocytes; mediastinal LAN uncommon; male predominance; good prognosis
Lymphocyte depleted	<1%	Diffuse fibrosis and large numbers of RS cells; older, male patients; disseminated at dx; seen in HIV; worst prognosis

- **Nonclassical HL** (5%): nodular lymphocyte predominant (NLP); involves peripheral LN
  80% present in stages I–II, Rx w/ RT vs. chemoRT w/ 4-yr PFS 88% and OS 96% (*JCO* 2008;26:434); consider rituximab because most NLP RS cells are CD20+
  Stages III–IV treated with combination chemo (vide infra)

Treatment

- **Stages I–II**: PET-adapted **ABVD** (doxorubicin, bleomycin, vinblastine, dacarbazine) ± RT
  Favorable: ABVD × 2–4 cycles ± RT (if PET ⊖ after 2 cycles reduce chemo or RT) Unfavorable (>50 y, bulky mediastinum, "B" sx, ESR >50, >3 nodal sites): ABVD × 4–6 + RT (stop at 4 cycles if PET ⊖ after 2 cycles)

- **Stages III–IV:** nivolumab (anti-PD-1)—AVD has superior PFS and AE profile compared with PET-adapted A-AVD (brentuximab vedotin [anti-CD30] + AVD) (*NEJM* 2024;391:1379)
- **Refractory/relapsed disease**: salvage chemo w/ PD-1 blockade + auto-HSCT ± RT
  PD-1/PD-L1 blockade (pembrolizumab or nivolumab) (*NEJM* 2015;372:311; *JCO* 2017;35:19)
  Brentuximab vedotin post-ASCT yields some long-term remissions (*Blood* 2016;128:1562)
- Late treatment effects include ↑ risk for:
  Second cancers: ~4.6× risk for up to 40 y (*NEJM* 2015;373:2499) *breast* (if RT), ∴ annual screening at age 40 or 8–10 y post-RT; *NHL*
  Cardiac disease (if RT or anthracycline): statin initiated prior to anthracycline ↓ risk of cardiac dysfunction (*JAMA* 2023;330:528)
  Pulmonary toxicity (if bleomycin); **hypothyroidism** (if RT), ∴ annual TSH (if neck RT)
- **International Prognostic Score** (IPS; *JCO* 2012;30:3383) risk factors: albumin <4 g/dL, Hb <10.5 g/dL, male gender, age >45 y, stage IV, WBC ≥15 k/μL, lymphocytes <600/μL or <8% of diff. 5-yr PFS 62–88% based on # of risk factors.

Non-Hodgkin Lymphoma (NHL)

Epidemiology and risk factors

- 79 types of NHL, ~70,000 new cases/y; median age dx 65 y; ♂ predom; 85% B-cell origin

WHO Classification of Lymphoid Malignancies (*Leukemia* 2022;36:1720)		
Type	**Examples**	**Associated Abnormalities**
Mature B cell → *aggressiveness*	Burkitt's lymphoma Diffuse large B-cell lymphoma (DLBCL) Mantle cell Marginal zone lymphoma (nodal, extranodal, splenic, cutaneous) Hairy cell leukemia (⊕ TRAP) Follicular lymphoma CLL/small lymphocytic lymphoma	*8q24, c-MYC* *BCL2, MYC, MLL2, CREBBP, etc.* *t(11;14) BCL1-IgH* → cyclin D1 *AP12-MALT1 & BCL-10-Ig enh* *BRAF V600E* *IGH-BCL2, MLL2, CREBBP* *IGHV, TP53, ATM, SF3B1, etc.*
Mature T cell & NK cell	Peripheral T-cell lymphoma Mycosis fungoides (cutaneous lymphoma)/ Sézary syndrome (+ LAN) Anaplastic large-cell lymphoma Angioimmunoblastic T-cell lymphoma	*TET2 and DNMT3A* Some *ALK1* ⊕

Treatment (*Lancet* 2017;390:298)

- Treatment and prognosis determined by histopathologic classification
- Rituximab (anti-CD20; *NEJM* 2012;366:2008) backbone of treatment if CD20+ (B cell)
- **Highly aggressive**
  Burkitt: dose-adjusted EPOCH-R (*NEJM* 2013;369:1915) or CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate, ifosfamide, etoposide, high-dose cytarabine, rituximab) (*Blood* 2008;112:2248). All Pts receive CNS (methotrexate) & tumor lysis syndrome prophylaxis.
  High-grade B-cell lymphoma w/ rearrangements of MYC and BCL2 ± BCL6: "double/triple-hit," assoc. w/ poor prognosis. Often use dose-adjusted EPOCH-R.

- **Aggressive subtypes:** goal is cure (*Am J Hematol* 2019;94:604)
  - DLBCL (most common lymphoma)
    - Int'l Prognostic Index (IPI; *Blood* 2007;109:1857): risk factors = age >60 y, stage III/IV, ≥2 extranodal sites, PS ≥2, LDH >nl; 4-yr OS 55–94%
    - Polatuzumab (anti-CD79b)-R-CHP (*NEJM* 2021;386:351) or R-CHOP (rituximab, cyclophosphamide, doxorubicin = hydroxydaunorubicin, vincristine = Oncovin, prednisone) (*NEJM* 2002;346:235 & 2008;359:613)
    - Statin prior to anthracycline (vide supra)
    - Early refractory/relapsed disease (<12 mo): proceed to **CAR-T** (qv)
    - Late relapse: salvage chemotherapy; CAR-T if no remission after chemo
    - Second relapse and beyond: novel immunotherapy such as bispecific antibodies
  - Mantle cell: variable clinical course, GI involvement common
    - Young/fit Pts: induction chemo ± BTKi followed by +rituximab maintenance
    - Old/unfit Pts: low-intensity chemo or BTKi + rituximab maintenance (*AJH* 2022;97:638)
- **Indolent subtypes:** localized disease may be curable with RT; with systemic disease focus is more on sx management and disease control rather than cure
  - Follicular lymphoma: 2nd most common lymphoma; active surveillance in asx Pts
    - Initial Rx: RT if localized, rituximab or obinutuzumab (anti-CD20) + chemo (bendamustine, CVP, lenalidomide) (*NEJM* 2017;377:1331)
    - T-cell engagers or CAR-T for subsequent therapy
  - Marginal zone lymphoma (MZL):
    - Includes nodal MZL, extranodal MZL of mucosal lymphoid tissue (MALT), splenic MZL
    - A/w chronic infection and autoimmune processes (*H. pylori* in gastric, HCV, Sjögren's)
    - *H. pylori* treatment essential to cure gastric MALT
    - Treatment: similar to follicular lymphoma (*NEJM* 2022;386:568)
  - Hairy cell leukemia: BRAF V600E ⊕ in >95% of cases. Cladribine + rituximab (*JCO* 2020;38:1527).
    - Early relapse (<24 mo) use vemurafenib + rituximab; late relapse (>24 mo) repeat 1st line (*NEJM* 2021;384:1810).

HIV-associated NHL (*Blood* 2006;107:13)

- HIV ⊕ imparts 60–100× relative risk
- NHL is an AIDS-defining malignancy along with Kaposi's, cervical CA, anal CA
- Concurrent HAART & chemotherapy likely provide survival benefit
- DLBCL & immunoblastic lymphoma: CD4 <100, EBV-associated. Burkitt lymphoma: can occur with CD4 >200. Avoid rituximab if CD4 <50.
- Primary CNS lymphoma: CD4 <50, EBV-assoc. (also seen in Pts w/o HIV). Rx w/ high-dose MTX-based regimen + steroid ± temozolomide ± RT, consider auto-HSCT.

Small Lymphocytic Lymphoma (SLL) or Chronic Lymphocytic Leukemia (CLL)

Definition (*NEJM* 2005;352:804; *Blood* 2008;111:5446)

- Monoclonal, functionally incompetent mature B lymphocytes; CLL & SLL = same disease
- CLL: >5000/µL malignant cells; SLL: <5000/µL malignant cells w/o LAN or splenomegaly
- Monoclonal B lymphocytosis: resembles but does not meet CLL criteria, observe

Epidemiology and risk factors

- >20,000 new cases/y; median age at dx is 71 y; most common adult leukemia

Clinical manifestations

- **Often asx** & identified by lymphocytosis on CBC; 10–20% p/w "B symptoms"
- **Lymphadenopathy** (80%) and **hepatosplenomegaly** (50%)

- **Autoimmune hemolytic anemia** (AIHA) (~10%) or **thrombocytopenia** (ITP) (~1–2%)
- Hypogammaglobulinemia ± neutropenia → ↑ susceptibility to **infections**
- Bone marrow failure in ~13%; monoclonal gammopathy in ~5%
- Aggressive **Richter's transformation** in ~5% into high-grade lymphoma (poor prognosis)

Diagnostic evaluation

- **CBC w/ diff**: **absolute lymphocyte count**
- **Peripheral smear: lymphocytosis** (predominantly mature-appearing small cells) "**smudge**" cells from damage to abnl lymphs from shear stress of making blood smear
- **Flow cytometry: clonality** with dim surface Ig; CD5+, CD19+, CD20+, CD23+
- Bone marrow (not req for dx): normo- or hypercellular; ≥30% small B lymphocytes
- **Genetics:** del(17p)/mutant TP53 = unfavorable; trisomy 12 neutral; del 13q14 and mut *IGHV* favorable. Nine significantly mutated genes, including *TP53, NOTCH1*, *MYD88*, and *SF3B1* (*NEJM* 2011;365:2497; *JCI* 2012;122:3432).

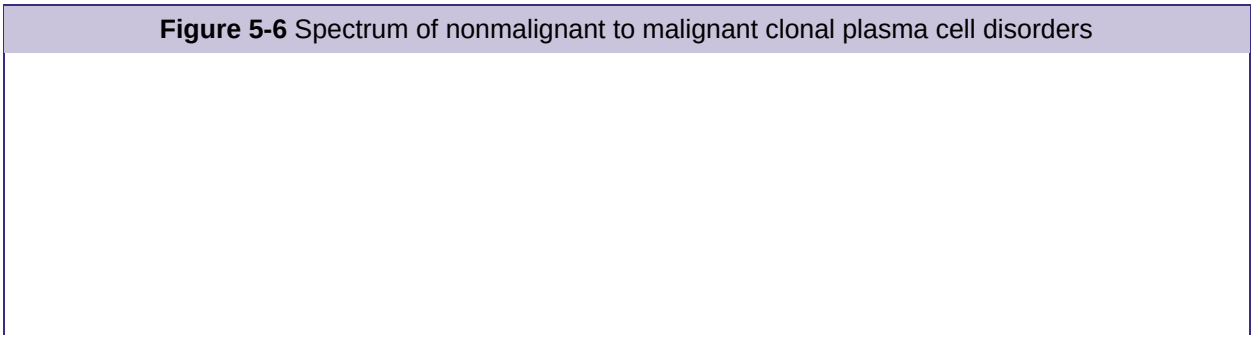
Rai System CLL Staging & Prognosis		
Stage	**Description**	**Median Survival**
0	Lymphocytosis *only*	>10 y
I	⊕ lymphadenopathy	7–10 y
II	⊕ hepatosplenomegaly	
III	⊕ anemia (not AIHA)	1–2 y
IV	⊕ thrombocytopenia (not ITP)	

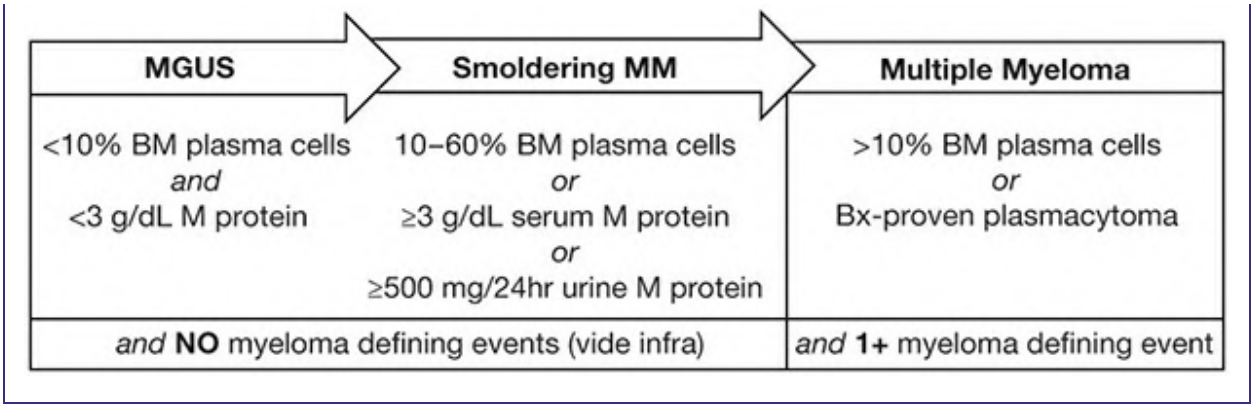
Treatment (*JAMA* 2023;329:918)

- Observation unless "active disease": Rai stage III/IV, disease-related sx, progressive disease, AIHA or ITP refractory to steroids, recurrent infections
- **First-line** (no consensus): BTK inhib (eg, acalabrutinib; requires long-term maintenance) *or* venetoclax + obinutuzumab (*NEJM* 2023;388:1739)
- Second-line & beyond: in general, choose Rx w/ mechanism different from 1st line Rx. BTK inhibitors (eg, zanubrutinib [*NEJM* 2023;388:319] or pirtobrutinib [*NEJM* 2023;389:33]), venetoclax. Consider allo-HSCT if refractory.
- HSCT is the only curative Rx but must balance Pt/disease characteristics and goals of care. Different rates of complete remission, time to progression, and toxicities.

PLASMA CELL DYSCRASIAS

Figure 5-6 Spectrum of nonmalignant to malignant clonal plasma cell disorders





Monoclonal gammopathy of uncertain significance (MGUS) (*NEJM* 2018;378:241)

- ✓ CBC, Ca, Cr, SPEP, serum free light chains, UPEP w/ immunofixation (to exclude MM)
- Close observation: repeat SPEP in 6 mo, then yearly thereafter if stable
- ~1%/y or ~25% lifetime risk → MM, WM, amyloidosis, or malign. lymphoproliferative dis.
- Abnormal serum free light chain ratio & M protein ≥1.5 g/dL: ↑ risk of progression to MM

Smoldering multiple myeloma

- CRAB criteria absent, but need whole-body MRI, PET-CT, or low-intensity CT survey to rule out occult bone lesions
- Risk of prog. 5%/y. Criteria predict risk of progression: M-protein >2 g/dL, BM plasma cells >20%, and FLC ratio >20 (*Blood Cancer J* 2018;8:59).
- Daratumumab (anti-CD38) shown to improve OS in high-risk SMM (*NEJM* 2025;392:1777)

Plasmacytoma (*Br J Haem* 2004;124:717)

- Solitary plasma cell tumor; often in bone but can be extra-osseous
- Managed w/ RT; ↑ risk of developing overt MM w/ bone lesions vs. extra-osseous lesions

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Multiple Myeloma (MM)

Definition and epidemiology (*Lancet* 2021;397:410)

- Malignant neoplasm of **plasma cells** producing a monoclonal Ig = "**M protein**"
- ~30,000 new cases/y; median age at diagnosis 69 y; more common in African Americans

Clinical manifestations (CRAB criteria and other less common features)

- Hyper**C**alcemia due to ↑ osteoclast activity
- **R**enal disease: multiple mechanisms include toxic effect of filtered light chains → *renal failure* (cast nephropathy) or *type II RTA;* amyloidosis or light chain deposition disease → *nephrotic syndrome*; hypercalcemia, urate nephropathy, type I cryoglobulinemia
- **A**nemia (normocytic) due to bone marrow involvement; rarely, may see AIHA
- Lytic **B**one lesions due to ↑ osteoclast activity → pathologic fx
- Recurrent infxns due to relative hypogammaglob. (clonal plasma cells suppress nl Ig)
- Neurologic: cord compression; POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes) syndrome
- Hyperviscosity: usually when IgM >4 g/dL, IgG >5 g/dL, or IgA >7 g/dL
- Coagulopathy: seen in amyloid due to binding & depletion of Factor X
- AL amyloidosis (see "Amyloidosis")

Diagnostic and staging evaluation (*Lancet Onc* 2014;15:e538)

- **Dx:** BM plasma cells ≥10% or bx-proven plasmacytoma & ≥1 **MM-defining event**:
  a. myeloma-related organ or tissue impairment (**ROTI**) = lytic bone lesions, Ca >11 mg/dL, C mg/dL, or Hb <10 g/dL
  b. any of the following biomarkers: BM plasma cells ≥60%, serum free light chain (FLC) ratio ≥100:1, >1 focal lesion on MRI

  Skeletal imaging (plain X-rays, MRI, CT survey, PET-CT) to identify lytic bone lesions and areas at risk for pathologic fracture
- **Variants**
  Plasma cell leukemia: plasma cell count >2000/μL in peripheral blood
  Nonsecretory MM (~2% of MM Pts; MM without M protein or FLC ratio abnormality)
- ✓ Peripheral smear for rouleaux, Ca, alb, Cr; ↓ anion gap, ↑ globulin, ↑ ESR
- **Protein electrophoresis and immunofixation**
  Serum protein electrophoresis (SPEP): quantitates M component; ⊕ in >80% of Pts Ddx of M component: MM, MGUS, CLL, lymphoma, sarcoidosis, RA Polyclonal hypergam seen in inflammatory states: HIV, rheumatic diseases, cirrhosis
  Urine protein electrophoresis (UPEP), total urine protein, or spot urine prot/Cr ratio useful for Pts who secrete only light chains (Bence-Jones proteins), as they are rapidly filtered
  Immunofixation: shows component is monoclonal and identifies Ig type → IgG (50%), IgA (20%), IgD (2%), IgM (0.5%), light chain only (20%), nonsecretors (<5%)
  Serum FLC assay: important for dx (esp. light chain-only Pts) and f/up response to Rx
- β_2-microglobulin (β_2M) and LDH levels reflect tumor burden
- **BM bx cytogenetics. Standard risk** = hyperdiploidy or t(11;14); **high risk** = hypodiploidy, del. 17p13 (~10% of Pts), t(4;14) & t(4;16).

Multiple Myeloma Staging Systems (*JCO* 2015;33:2863)

Stage	R-ISS Criteria	5-year OS
I	β_2M <3.5 mg/L, albumin >3.5 g/dL, no high-risk cytogenetic features, AND normal LDH	82%
II	Not stage I or III	62%
III	β_2M >5.5 mg/L AND High-risk cytogenetics or Elevated LDH	40%

Treatment and prognosis (*NEJM* 2016;375:754 & 1319; 2018;378:518 & 379:1811)

- Decisions dictated by risk stratification and transplant eligibility; generally incurable. Stratify by R-ISS which includes chrom abnl & LDH (*JCO* 2015;61:2267).
- Rx incl. **proteasome inhibitors:** bortezomib (V), carfilzomib (K), ixazomib (I) **immunomodulators:** lenalidomide (R), thalidomide (T), pomalidomide (P) **immunoRx:** daratumumab, isatuximab (anti-CD38), elotuzumab (anti-SLAMF7, Elo), CAR-T or bispecific targeting BCMA or GPRC5D other active drugs: dexamethasone (D), melphalan, panobinostat, cyclophosphamide
- **Induction Rx**: V, R, D + anti-CD38 (dara or isa) quad Rx (Dara or Isa-RVD) improves response rates (*NEJM* 2024;390:301 & 2024;391:1597). Triplet therapy used if frail or sometimes those with standard risk disease.
- If *not* transplant eligible: **induction Rx** ↑ survival, not curative; maint chemo typically used
- If transplant *eligible:* consider immediate **high-dose melphalan** + **auto-HSCT** following induction vs. harvest HSCs and defer transplant to later line of therapy. Not curative, but ↑ progression-free survival (PFS) vs. chemo alone (*NEJM* 2014;371:895; *Lancet Onc* 2015;16:1617). Maint Rx w/ R improves PFS/OS (*NEJM* 2014;371:10). Timing of HSCT (upfront vs. relapse) debatable.
- 1st Relapse/refractory: HSCT (if good prior response, no prior HSCT); no consensus for

chemotherapy regimen, various combinations of the front-line classes acceptable
- 2nd Relapse or later: CAR-T or bispecific Ab (*NEJM* 2022;387:495 & 2232)
- Fracture ppx: **bisphosphonates** (*JCO* 2007;25:2464), denosumab esp. w/ renal disease *renal:* consider plasmapheresis for acute renal failure *hyperviscosity syndrome:* plasmapheresis; *recurrent infxns:* consider IVIG
- Common **toxicities** of Rx: melphalan → myelosuppression; lenalidomide/pomalidomide → low plts & thromboembolism (use ASA ppx); bortezomib → periph. neuropathy; carfilzomib → cardiopulmonary

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Waldenström's Macroglobulinemia (WM)

Definition (*Blood* 2009;114:2375; *NEJM* 2012;367:826)

- B-cell neoplasm (lymphoplasmacytic lymphoma) that secretes monoclonal IgM
- >90% w/ *MYD88* (NF-κB pathway) L265P mutation; 30–40% CXCR4 mutants
- *No evidence of bone lesions* (IgM M component + lytic bone lesions = "IgM myeloma")

Clinical manifestations

- **Fatigue** from anemia is most common sx; also night sweats, weight loss, and fevers
- **Tumor infiltration:** BM (cytopenias), hepatomegaly, splenomegaly, lymphadenopathy
- **Circulating monoclonal IgM**
  - **Hyperviscosity syndrome** (higher risk w/ IgM ≥3000): *Neurologic:* blurred vision ("sausage" retinal veins), HA, dizziness, ΔMS. *Cardiopulmonary:* CHF, pulm. infiltrates.
  - Type I **cryoglobulinemia → Raynaud's phenomenon**
  - Acquired vWD → Platelet dysfxn → mucosal bleeding
- **IgM deposition** (skin, intestine, kidney); amyloidosis and glomerulopathy
- **Autoantibody activity of IgM:** *Warm or cold AIHA* (prominent **rouleaux**; 10% Coombs ⊕ = AIHA). *Peripheral neuropathy:* may be due to anti-myelin-associated glycoprotein IgM.

Diagnostic evaluation

- SPEP + immunofixation with IgM monoclonal spike (any level)
- BMBx: ↑ plasmacytoid lymphocytes; β_2M, age and LDH are prognostic (MSS-WM)
- **Relative serum viscosity:** ratio serum viscosity to H_2O (nl 1.8); hyperviscosity when >5–6

Treatment

- Asx Pts should be monitored; similar survival to age/sex-matched population
- Hyperviscosity: **plasmapheresis;** limit transfusions if possible (worsen hyperviscosity)
- Sx (eg, progressive anemia): chemoimmunotherapy, BTK inhibitors, BCL2 antagonists

HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

Transplantation of donor pluripotent cells that can reconstitute all recipient blood lineages

Categories of Stem Cell Transplantation		
Feature	**Allogeneic (Allo)**	**Autologous (Auto)**
Donor–recipient relationship	Immunologically distinct	Donor is also recipient
Graft-vs.-host disease	***Yes***	***No***

Graft-vs.-tumor effect	***Yes***	***No***
Risk of graft contam. w/ tumor	No	Yes
Relapse risk (leukemia)	Lower	Higher
Transplant-related mortality	***Higher***	***Lower***

Indications (*BBMT* 2015;21:1863; *BMT* 2015;50:1037)

- **Malignant disease**
  - **Auto-HSCT** allows *high-dose myeloablative chemo* and then rescue what would be otherwise lethal cytopenias with autologous stem cells. Used in chemosensitive diseases such as relapsed/refractory DLBCL, MM, testicular germ cell tumor.
  - **Allo-HSCT** produces **graft-vs.-tumor** (GVT) effect, in addition to hematopoietic rescue (used for AML, ALL, MDS, CML-blast crisis, lymphoma)
- **Nonmalignant disease:** allo-HSCT replaces abnl lymphohematopoietic system w/ one from nl donor (eg, immunodeficiencies, aplastic anemia, hemoglobinopathies)

Allo-HSCT

- **Types:** *based on donor/recipient matching of major HLA antigens on Chr. 6* (4 principal genes for serotyping: *HLA-A*, *-B*, *-C*, & *-DR*; each w/ 2 alleles ∴ 8 major Ag) *Matched related* (MRD, sibling 8/8 major Ag match): lowest GVHD; **preferred donor**
  - *Matched unrelated (MUD):* ↑ risk of GVHD; ∴ matching of 10 HLA alleles (*DQ* also) to ↓ risk; chance of match correlates w/ ethnicity (*NEJM* 2014;371:339) *Mismatched related* (eg, 1/8 Ag mismatch): ↑ available donor pool, but ↑ GVHD, rejection; ∴ need additional immunosuppression
  - *Haploidentical*: typically, between parents and young children or sibs (“half” match); early post-tx cyclophosphamide reduces GVH by destroying proliferating alloreactive T cells
  - *Umbilical cord blood:* HSC processed at birth & stored. Yields lower cell number. Need 2 cords per adult. Neonatal immune cells: HLA-mismatch tolerated better, ↓ GVHD, slow immune reconstitution → ↑ late viral infections (*Blood* 2010;116:4693).
- **Graft-vs.-host disease (GVHD):** *undesirable* side effect of allo-HSCT allogeneic T cells view host cells as foreign; ↑ incid. w/ mismatch or unrelated donors
- **Graft-vs.-tumor (GVT):** *desired* effect in allo-SCT; graft T cells attack host tumor cells

Transplantation procedure (for allo-HSCT)

- **Pre-Txp conditioning regimen goal:** immunosuppression to allow donor cell engraftment & anti-tumor efficacy to ↓ relapse risk. Type and dose of agents determine this balance. PT-Cy emerging as preferred GVHD ppx (*JCO* 2024;42:28).
  - *Myeloablative conditioning*: high-dose chemo and/or total body irradiation. Low relapse rates, high immunosuppression, higher transplant-related morbidity.
  - *Reduced-intensity conditioning (“RIC”)*: lower dose of chemo → ↓ transplant-related morbidity/mortality, but ↑ relapse b/c it relies more on GVT effect (*Blood* 2015;126:23). Allows allo-HSCT for older adults (>60) or Pts w/ comorbidities.
- **Sources of hematopoietic stem cells** (*NEJM* 2012;367:1487)
  - *Peripheral blood stem cells (PBSC)*: easier to collect, more commonly used. BM vs. PBSC ≈ survival; BM ↓ chronic GVHD, PBSC ↓ graft failure, faster engraftment.
  - *Bone marrow (BM):* original source, preferred in non-malignant disease, ↓ GVHD rates
  - *Umbilical cord blood stem cells (UCB):* see above in “Types” under “Allo-HSCT”
- **Engraftment:** absolute neutrophil count (ANC) recovers to 500/µL w/in ~2 wk w/ PBSC, ~2.5 wk w/ BM, ~4 wk w/ UCB. G-CSF accelerates recovery by 3–5 d in all scenarios.

Complications

- Either **direct chemoradiotoxicities** associated with preparative regimen or consequences of **interaction between donor and recipient immune systems**
- **Engraftment syndrome**: fever, rash, noncardiogenic pulm. edema, abnl LFTs, AKI, wt gain. Dx of exclusion: r/o infection, GVHD. Rx w/ 1 mg/kg steroids, rapid taper over 3–4 d.
- **Sinusoidal obstruction syndrome (SOS):** incidence ~10%, mortality ~30%
  - Mechanism: direct injury to hepatic venules → *in situ* thrombosis; consider with busulfan
  - Symptoms: tender hepatomegaly, ascites, rapid weight gain, jaundice, fluid retention with severe disease → liver failure, encephalopathy, hepatorenal syndrome
  - Diagnosis: ↑ ALT/AST, ↑ bilirubin; ↑ PT with severe disease; Doppler U/S *may* show reversal of portal vein flow; ↑ hepatic wedge pressure; abnl liver bx
  - Treatment: supportive; prophylaxis with **ursodiol;** treat w/ defibrotide (*Blood* 2016;127:1656)
- **Idiopathic pneumonia syndrome (IPS):** 5–25% of Pts, >50% mortality (*Blood* 2003;102:2777)
  Alveolar injury 2/2 direct toxicity → fever, hypoxia, diffuse infiltrates; occult infxn frequent
- Cryptogenic organizing pneumonia (COP): w/in 2–6 mo; severe alveolar inflammation → fevers, cough w/ alveolar consolidations on CXR. Rx = steroids (*J Transl Med* 2016;14:169).
- **Diffuse alveolar hemorrhage (DAH):** Dx: bronchoscopy to exclude infection; ↑ bloody lavage fluid. Rx: 500–1000 mg Solu-Medrol × 3 d ± etanercept (*BBMT* 2015;1:67).
- **Acute GVHD** (usually within 6 mo of transplant; *NEJM* 2017;377:2167)
  - Clinical grades I–IV based on scores for **skin** (severity of maculopapular rash), **liver** (bilirubin level), and **GI** (volume of diarrhea); bx supports diagnosis
  - Prevention: **immunosuppression** (MTX + cyclosporine, or tacrolimus), T-cell depletion of graft, post-Tx cyclophosphamide (*JCO* 2024;42:3277)
  - Tacrolimus toxicity: PRES, TMA, renal toxicity → check daily levels
  - Treatment: grade I → topical Rx; grades II–IV → associated with ↓ survival and ∴ treated with immunosuppressants (corticosteroids, CsA, tacrolimus, rapamycin, MMF)
- **Chronic GVHD** (developing or persisting >3 mo posttransplant; *NEJM* 2017;377:2565)
  - Clinical: malar rash, sicca syndrome, arthritis, obliterative bronchiolitis, bile duct degeneration, cholestasis, and many others. More common w/ PBSC than BM.
  - Treatment: see aGVHD; rituximab; photopheresis; ibrutinib (*Blood* 2017;130:21), ruxolitinib (*NEJM* 2021;385:228), belumosudil (*Blood* 2021;138:2278), axatilimab (*NEJM* 2024;391:1002)
- **Graft failure**
  - Primary = persistent neutropenia without evidence of engraftment
  - Secondary = delayed pancytopenia after initial engraftment; either immune mediated via immunocompetent host cells (**graft rejection**) or non-immune mediated (eg, CMV)
- **Infectious complications**
  - due to regimen-induced pancytopenia and immunosuppression
  - both primary infections and reactivation events occur (eg, CMV, HSV, VZV)

Timing of Complications Following Allogeneic HSCT			
	Time After Transplant and Associated Risk Factors		
	Days 0–30 Mucositis; organ dysfunction; neutropenia	**Days 30–90** Acute GVHD; ↓ cell immunity	**>90 Days** Chronic GVHD; ↓ cellular & humoral immunity
Viral infection	Respiratory and enteral viruses, BK virus		
	CMV		
		EBV-related lymphoma, HHV 6 & 7	
			VZV*, HSV, JC
Bacterial infection	Gram ⊕ cocci (*Staph., Strep. viridans*) GNRs (Enterobacteriaceae, *Pseudomonas, Legionella, S. maltophilia*)		Encapsulated bacteria, site-specific infection (UTI, CAP, SSTI)
Fungal infection	*Candida* spp.		
	Aspergillus spp.		
Parasitic infection		*T. gondii* *P. carinii* *S. stercoralis*	*T. gondii* *P. carinii*
Regimen-related	Pancytopenia		Growth failure
	Mucositis, rash, alopecia		Hypogonadism/infertility
	Nausea, vomiting, diarrhea		Hypothyroidism
	TMA, PRES		Cataracts
	Hemorrhagic cystitis		Avascular necrosis of bone
	Veno-occlusive disease		2nd malignancy
	IPS/Interstitial pneumonitis		
Immune mediated	Acute GVHD		Chronic GVHD
	Primary graft failure	Secondary graft failure	

*Primarily among persons who are seropositive before transplant

Prophylaxis/Supportive Medications During HSCT		
Medication	**Prophylaxis Against**	**Duration**
Fluconazole	*Candida*	75 d
Acyclovir	HSV/VZV	365 d
Valganciclovir, ganciclovir, or letermovir if CMV ⊕	CMV	100 d or when no longer immunosuppressed
Antibiotics (eg, fluoroquinolone)	Bacterial infxn	While neutropenic
TMP–SMX or atovaquone	PCP	365 d or when off immunosupp.
Allopurinol	Hyperuricemia	Until d –1

IMMUNOTHERAPY & CELLULAR THERAPY

Immune Checkpoint Inhibitors (ICI)

Overview (*Science* 2018;359:1350)

- Immune checkpoints: coinhibitory signaling molecules that limit immune responses
- Cytotoxic T-lymphocyte-assoc. protein 4 (CTLA-4): ↓ T-cell activation via negative signals and ligand competition w/ CD28 (activating co-stim. molecule)
- Programmed cell death protein 1 (PD-1): on activated T cells, turns off T-cell responses
- Prog. death-ligand 1 (PD-L1): PD-1 ligand expressed on tumor and/or immune cells

ICIs (*Ann Oncol* 2017;28:2377)

Target	Drugs	Select Indications	Common Immune-Related Adverse Events (IRAE)
PD-1	Nivolumab Pembrolizumab Cemiplimab Dostarlimab	Melanoma, NSCLC, RCC, HNSCC, esoph., endometrial, MSI-high tumors	Rash (12%); hypothyroid (5%); pneumonitis (2%); colitis (<1%); hepatitis (<1%); type 1 DM (<1%)
PD-L1	Atezolizumab Avelumab Durvalumab	Urothelial carcinoma, NSCLC, SCLC, HCC (atezo)	Rash (5%); hypothyroid (2%); adrenal insufficiency (<1%); colitis (<1%); pneumonitis (<1%)
CTLA-4	Ipilimumab	Melanoma, RCC (w/ PD-1), mesothelioma (w/ PD-1)	Rash (21%); colitis (5%); hypophysitis (1%); hypothyroid (1%); pneumonitis (<1%); hepatitis (<1%)

- ICIs can cause inflammation of any tissue (lungs, liver, colon, joints, skin, etc.)
- Rare: myocarditis (can be fulminant), myositis, myelitis, uveitis, diabetes
- Workup: CT chest for dyspnea; colonoscopy and infectious workup for colitis; TSH, FT4, a.m. cortisol, glucose. Trend comprehensive metabolic panel and TSH while on ICI.
- IRAEs graded 1 (mild) to 4 (severe) (*Nat Rev Dis Primers* 2020;6:38; *Curr Cardiol Rep* 2021;23:98)

ICI toxicity treatment (multidisciplinary care)

- Mild sx (grade 1): supportive care, can often continue Rx; moderate sx (grade 2): hold ICI, consider steroids; severe sx (grades 3–4): often requires admission to hospital, hold ICI, IV steroids, targeted therapies (eg, etanercept)
- Endocrinopathies (hypophysitis, hypothyroid) are not reversible; Rx hormone replacement
- Managing IRAEs with steroids likely does not reduce ICI efficacy (*J Clin Oncol* 2019;37:1927)

Chimeric Antigen Receptor (CAR)-T Cells & Bispecific Ab

Overview (*Nat Rev Cancer* 2021;21:145; *Nat Rev Drug Disc* 2024;23:301)

- **CAR-T:** autologous T cells w/ chimeric receptor that is antibody variable region fused to T-cell costimulatory intracellular signaling domains → MHC-independent Ag recognition. Requires lymphodepletion with busulfan and/or cyclophosphamide.
- **Bispecific antibodies**: simultaneously engages and activates TCR on T cells and binds an epitope on cancer cells to induce anticancer activity

Toxicities

- **Cytokine release syndrome (CRS)**: fever, HoTN, shock secondary to overwhelming cytokine release from proliferating T cells
- **Immune effector cell–associated neurotoxicity synd. (ICANS)**: cerebral edema → HA, aphasia, delirium, lethargy/obtundation. Graded using ICE score (vide infra).
- **Other:** B-cell aplasia in setting of CD19-directed therapy; secondary malignancy (*Blood* 2024;143:2099) including T-cell lymphoma (*NEJM* 2024;391:1217; *Nat Med* 2024;30:984)

CAR-T Toxicity (*Biol Blood Marrow Transplant* 2019;25:625)			
Type	**Grade**	**Mechanism & Manifestations**	**Treatment**
CRS	1	Fever (≥38°C) ± other sx	Supportive (fluids, O_2), ± steroids ± anti-IL-6 (tocilizumab or siltuximab), depending on severity
	2	Fever + HoTN not needing pressors ± O_2 by nasal cannula	
	3	Fever + pressor ± O_2 > nasal cannula	
	4	Fever + >1 pressor ± ⊕ pressure vent	
ICANS	1	ICE 7–9 pts	Steroids, anticonvulsants for seizures
	2	ICE 3–6 pts	
	3	ICE 0–2 pts	
	4	Unarousable & unable to perform ICE	

ICE score: orientation (4 pts), name 3 objects (3 pts), follow commands (1 pt), write sentence (1 pt), count backward from 100 by 10 (1 pt)

LUNG CANCER

Epidemiology and risk factors

- Most common cause of cancer-related death for both men and women in the U.S.
- Two main types: **non–small cell** (NSCLC, ~85% of cases); **small cell** (SCLC, ~15%)
- **NSCLC** comprised of **adeno** (40%), **squamous cell** (SCC, 20%), & large cell (5%) carcinomas, as well as other/not classified (20%)
- **Cigarette smoking:** 85% of lung cancers occur in smokers; risk ∝ total pack-yrs, ↓ risk after quitting/reducing but not to baseline (*Int J Cancer* 2012;131:1210). SCC & SCLC almost exclusively in smokers, adeno most common type in nonsmokers.
- Asbestos: when combined with smoking, synergistic ↑ in risk of lung cancer
- Other: RT (for other cancer); HIV; environ. toxins (radon, 2nd-hand smoke); pulm. fibrosis

Screening (*JAMA* 2021;325:962)

- **Annual low-dose chest CT** in ≥20 pack-year current or former (quit w/in 15 y) smokers, age 50–80 y → 20% ↓ lung cancer–related mortality (*NEJM* 2020;382:503)
- High rates of screen-detected nodules. Multidisciplinary mgmt recommended (pulm., med onc, thoracic radiology, & surgery).

Clinical manifestations

- ~10% asymptomatic at dx, detected incidentally (only 16% w/ localized dis. at presentation)

- **Endobronchial growth** of 1° tumor: **cough**, **hemoptysis**, **dyspnea**, pain, wheezing, post-obstructive pneumonia; more common with squamous or small cell (central location)
- **Regional spread**: can cause dysphagia (esophageal compression), stridor (tracheal obstruction), hoarseness (recurrent laryngeal nerve palsy). Pleural effusions & pleural metastases specifically = metastatic disease = Stage IV. **Pancoast's syndrome:** apical tumor → brachial plexus involvement (C8, T1, T2) → Horner's syndrome, shoulder pain, rib destruction, atrophy of hand muscles **SVC syndrome** (*NEJM* 2007;356:1862): central tumor → SVC compression → face/arm swelling (>80%), neck/chest vein distention (~60%), SOB/cough (~50%), HA (~10%); Rx = steroids, diuretics, RT ± chemo, SVC stent if severe sx, anticoag if clot
- **Extrathoracic metastases:** brain (~25% of patients at dx), bone, liver, adrenal
- **Paraneoplastic syndromes**
  Endo: **SIADH** (SCLC); ACTH (SCLC) → **Cushing's;** PTH-rP (SCC) → **hyperCa**
  Skeletal: digital clubbing (NSCLC), **hypertrophic pulm. osteoarthropathy** (adenocarcinoma) = symmetric polyarthritis and proliferative periostitis of long bones
  Neuro (SCLC): **Lambert–Eaton** (anti-P/Q-type voltage-gated Ca^{2+} channel Abs), peripheral neuropathy (anti-Hu, anti-PCA-2, anti-CRMP5), cerebellar degeneration (anti-Hu, anti-Yo, anti-Ri, anti-Tr), encephalomyelitis (anti-Hu, anti-Ma1/2, anti-CRMP5)
  Hematologic: hypercoagulable state (adenocarcinoma), DIC

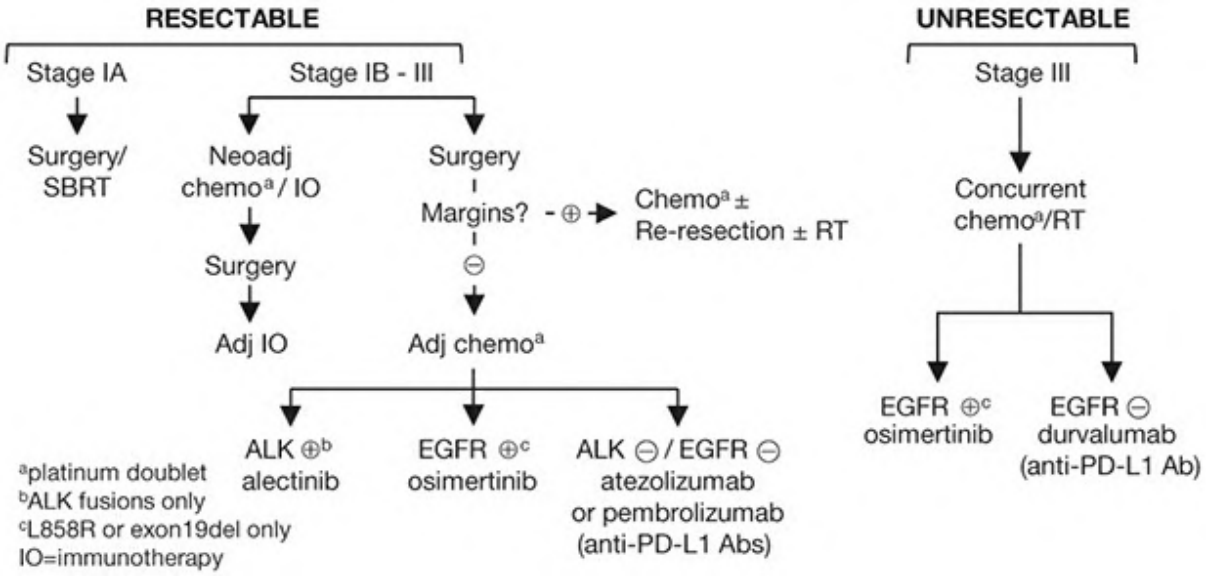
Diagnostic and staging evaluation

- **Staging:** based on tumor size and extent of invasion (T), regional LN involvement [N: N0 (none), N1 (ipsilat. hilar), N2 (ipsilat. mediast.), N3 (contralat., supraclav.)] and presence of metastases (M) (*Chest* 2017;151:193). Pleural effusions/implants = stage IV.
  5-y survival: ~70–90% for stage I, 50–60% stage II, 15–35% stage III, 0–10% stage IV (*J Thorac Oncol* 2016;11:39); survival improving with newer therapies (*NEJM* 2020;383:640)
- **Imaging: CT w/ contrast** of chest & abd/pelvis to assess for mets (adrenal, liver, bones).
  PET-CT more Se than CT alone for detecting mediastinal, bone, and distal mets (*NEJM* 2009;361:32). **Brain MRI** for all Pts except stage IA.
- **Pathology:** via **bronchoscopy** (central lesions) or **CT-guided needle bx** (peripheral lesions or accessible sites of suspected metastasis); mediastinoscopy (LN bx/eval), VATS (eval. of pleural peripheral lesions), thoracentesis if pleural effusion (cytology)
- **Genetics** (usually just in adv/metastatic disease)**:** ✓ *EGFR* (include in stage IIA-IIIB), *ALK, ROS1, MET, KRAS, RET, BRAF, ERBB2, NTRK* fusion for all non-squamous disease (incidence lower in SCC but still recommend testing); PD-L1 expression
- PFTs w/ quant V/Q if Rx includes resection; need 30% nl predicted lung fxn *after* resection

NSCLC Treatment (*Lancet* 2021;398:535)

- Localized disease: surgery if possible; RT (eg, stereotactic ablative radiotherapy [SABR]) vs. chemo/RT if not (see Figure 5-7)
- Neoadjuvant & periop ICI w/ chemo ↑ event-free survival (*NEJM* 2023;389:491 & 1672)
- Metastatic disease: targeted Rx can substantially improve survival & are better tolerated (see Stage IV Rx table); however, 5-y survival still poor. First-line immunotherapy (IO) ± chemo for most Pts w/o targetable mutations. Pemetrexed + pembrolizumab often continued as maintenance when used. Palliative care ↑ survival (*NEJM* 2010;363:733); palliative RT for local sx from tumor/mets.
- Solitary brain metastasis (oligomet): surgical resection + brain radiation may ↑ survival

Figure 5-7 Localized NSCLC treatment algorithm



(*Lancet* 2023;402:451; *NEJM* 2023;389:137; 390:1265 & 1756;391:585)

Stage IV NSCLC Treatment			
Type	**Genetics**	**%**	**Treatment**
Adeno or Other	*EGFR* L858R or ex19del	~15	1st line: osimertinib w/ or w/o chemo (*NEJM* 2018;378:113; 2023;389:1935) or amivantamab–lazertinib (*NEJM* 2024;391:1486)
	EGFR ex20 insertion	2–3	Subsequent Rx w/ amivantamab (*NEJM* 2023;389:2039) after platinum chemo
	ALK fusions	~4	Lorlatinib (*NEJM* 2020;383:2018) or alectinib (*NEJM* 2017;377:829)
	ROS1 fusions	2	1st line: entrectinib, repotrectinib (*NEJM* 2024;390:118), or crizotinib
	MET ex14 skip or amplif.	3	Capmatinib (*NEJM* 2020;383:944) or tepotinib (*NEJM* 2020;383:931)
	RET fusions	1	Selpercatinib (*NEJM* 2023;389:1839) or pralsetinib (*Lancet Onc* 2021;22:959–969)
	BRAF V600E	1–3	Dabrafenib + trametinib or encorafenib + binimetinib
	NTRK fusions	<1	Larotrectinib (*NEJM* 2018;378:731) or entrectinib
	KRAS G12C	~13	Subsequent Rx w/ sotorasib or adagrasib (*NEJM* 2021;384:2371)
	PD-L1 ≥50%	30	Pembrolizumab or chemo + pembro (*NEJM* 2018;378:2078)
	ERBB2 muts.	1–2	Subseq. Rx w/ trastuzumab deruxtecan (*NEJM* 2022;386:241)
	No targets & PD-L1 <50%		Chemo (carbo/pemetrexed) + pembro (*NEJM* 2018;378:2078) or carbo/paclitaxel + anti-VEGF Ab (bevacizumab) + atezo (*NEJM* 2018;378:2288)
Squam	PD-L1 ≥50%		Pembrolizumab or chemo + pembro (*NEJM* 2016;375:1823)
	PD-L1 <50%		Chemo (carbo/paclitaxel) + pembro (*NEJM* 2018;379:2040)

Many are specific tyrosine kinase inhibitors ('tinibs) directed against EGFR, ALK, etc. Amivantamab is EGFR-MET bispecific mAb. Pembrolizumab is mAb against PD-1 on lymphocytes (ie, immune checkpoint inhibitor).

SCLC staging and treatment

- SCLC usually disseminated at presentation; poor overall survival
- Can be very responsive to chemotherapy, but rapidly develops resistance
- **Diagnosis:** all have Rb & p53 mutations (*Nature* 2015;524:47); 90% w/ neuroendo markers
- **Staging:**
  Limited stage (LS-SCLC): confined to ipsilat. hemithorax; within single radiation field Extensive stage (ES-SCLC): beyond single radiation field
- **Treatment:**
  - LS-SCLC: surgery followed by adj. chemo *or* concurrent RT + chemo followed by adj. durvalumab (*NEJM* 2024;391:1313)
  - ES-SCLC: primarily chemo (platinum + etoposide); adding atezolizumab ↑ survival (*NEJM* 2018;379:2220)
- **Prophylactic cranial irradiation** (PCI) controversial. Offered to potentially ↑ survival for LS-SCLC in complete remission (*NEJM* 1999;341:476). Role in ES-SCLC being studied.
- **Second line**: low response rates, short survival. Options: tarlatamab [DLL3 × CD3 bispecific T-cell engager] (*NEJM* 2023;389:2063), single-agent chemo (eg, lurbinectedin, topotecan, irinotecan), reRx w/ platinum doublet, anti-PD-1 (eg, nivo).

BREAST CANCER

Epidemiology

- In U.S., most common cancer in women; 2nd leading cause of cancer death in women
- **Genetic risk:** 15–20% ⊕ FHx → 2× ↑ risk; ~45% familial cases a/w germline mutation.
  BRCA1/2*:** 35–85% lifetime risk of breast ca. Germline loss-of-function mutations in ***PALB2 a/w 35% ↑ risk of breast cancer by age 70. Moderate risk mutations ***CHEK2*** and ***BARD1*** a/w 15–30% lifetime risk of breast cancer (*NEJM* 2021;384:428).
- **Estrogen:** ↑ risk with early menarche, late menopause, late parity or nulliparity (*NEJM* 2006;354:270); ↑ risk with prolonged HRT (RR = 1.24 after 5.6 y; *JAMA* 2003;289:3243); OCP use a/w extremely low to no ↑ risk (*NEJM* 2017;317:2228; *JAMA Oncol* 2018;4:516)
- Benign breast conditions: ↑ risk if atypia (atypical ductal or lobular hyperplasia; *NEJM* 2015;372:78) or proliferative (ductal hyperplasia, papilloma, radial scar, or sclerosing adenosis) features; *no* ↑ risk w/ cysts, simple fibroadenoma, or columnar changes
- ↑ risk with h/o ionizing radiation to chest for treatment of Hodgkin lymphoma

Prevention (if high risk: eg, FHx, LCIS, atypical hyperplasia)

- Tamoxifen (contraindic. in preg): ↓ risk contralateral breast ca as adjuvant Rx. Approved for 1° prevent. if ↑ risk: ↓ invasive breast cancer, but ↑ DVT & uterine ca.
- Raloxifene (only if post-menopausal): ↓ risk of invas breast ca, vertebral fx, & uterine ca, ↑ risk stroke & DVT/PE (*NEJM* 2006;355:125); less effective than tamoxifen for prevention
- Aromatase inhib. (post-menopausal): ↓ risk >50% (*Lancet* 2014;383:1041), ↑ osteoporosis
- *BRCA1/2* ⊕: intensified surveillance vs. prophylactic bilat. mastectomy which ↓ risk ~90%; bilat. salpingo-oophorectomy ↓ risk of ovarian *and* breast cancer (*NEJM* 2016;374:454)

Clinical manifestations

- Breast mass (hard, irregular, fixed, nontender), nipple discharge (higher risk if unilateral, limited

to 1 duct, bloody, associated with mass)
- Special types: **Paget** disease → unilateral nipple eczema + nipple discharge; **inflammatory** breast cancer → skin erythema and edema (*peau d'orange*)
- Metastases: lymph nodes, bone, liver, lung, brain

Screening (*JAMA* 2015;314:1599; *Annals* 2019;170:547)

- **Mammography:** ~20–30% ↓ **in breast cancer mortality**, smaller abs. benefit in women <50 y (*JAMA* 2018;319:1814); digital breast tomosynthesis (3-D) ↑ specificity (*JAMA Oncol* 2019;5:635); suspicious findings: clustered **microcalcifications**, **spiculated**, **enlarging**
- ACS: annual mammo starting at 45 (consider biennial after 54), cont. if life expect ≥10 y
- USPSTF: screen biennially ages 50–75 (some may want to begin at 40)
- ↑ risk: screen earlier w/ exam and mammo (age 25 in *BRCA1/2* carrier, 5–10 y before earliest FHx case, 8–10 y after thoracic RT, upon dx of ↑ risk benign disease)
- **MRI:** superior to mammo in high-risk and young Pts; consider annually if >20% lifetime risk (eg, ⊕ FHx, *BRCA1/2*, prior chest RT) (*Lancet* 2011;378:1804)
- **Germline genetic testing:** based on family history

Diagnostic evaluation

- **Palpable breast mass:** age <30 y → observe for resolution over 1–2 menstrual cycles; age <30 y, unchanging mass → **U/S** → aspiration if mass not simple cyst;
  age >30 y *or* solid mass on U/S *or* bloody aspirate *or* recurrence after aspiration → **mammo** (detect other lesions) *and* either **fine-needle asp.** or **core-needle bx**
  clearly cancerous on exam or indeterminate read or atypia on bx → **excisional bx**
- **Suspicious mammogram** with normal exam: stereotactically guided bx
- MRI: detects contralateral cancer in 3% of Pts w/ recently dx breast cancer & contralateral mammo (but PPV only 21%) (*NEJM* 2007;356:1295); utility remains unclear

Staging

- **Anatomic:** tumor size, chest wall invasion, axillary LN mets (*strongest prognostic factor*)
- **Histopathologic:** type (little prognostic relevance) & grade; lymphatic/vascular invasion
  In situ carcinoma: no invasion of surrounding stroma
  Ductal (DCIS): ↑ risk of invasive cancer in *ipsilateral* breast (~30%/10 y)
  Lobular (LCIS): benign entity; marker of ↑ risk of inv. cancer in *either* breast (~1%/y)
  Invasive carcinoma: infiltrating ductal (70–80%); invasive lobular (5–10%); tubular, medullary, and mucinous (10%, better prognosis); papillary (1–2%); other (1–2%)
  Inflammatory breast cancer (vide supra): not a histologic type but a clinical reflection of tumor invasion of dermal lymphatics; very poor prognosis
  Paget disease (vide supra): ductal cancer invading nipple epidermis ± associated mass
- **Tissue biomarkers:** estrogen and progesterone receptor (ER/PR), HER2
- Oncotype DX 21-gene expression recurrence score predicts which ER ⊕, HER2 ⊖ will have minimal benefit from adjuvant chemo in LN ⊖ (*NEJM* 2018;379:111) and LN ⊕ (1–3) disease (*NEJM* 2021;385:2336)

Simplified Staging & 5-y Dis.-Specific Survival (*CA Cancer J Clin* 2017;67:290; SEER 2017)

Stage	Characteristics	Description	5-y DSS
I	Tumor ≤2 cm	Operable locoregional	99%
IIA	Tumor >2 cm or *mobile* axillary nodes		98%
IIB	Tumor >5 cm or 2–5 cm w/ mobile nodes		96%
IIIA	Internal mammary or *fixed* axillary nodes	Locally advanced	95%
IIIB/C	Chest wall, skin, infra or supraclavic. nodes	Inoperable	80–85%

IV	Distant metastases	Metastatic	27%

General Approach to Treatment (*JAMA* 2019;321:288 & 1716)	
DCIS	**Mastectomy or lumpectomy ± RT ± chemoprevention** (*Lancet* 2016;387:849 & 866)
I	Surgery + RT (↓ local recurrence, no ▵ survival in ER/PR ⊕; *NEJM* 2023;388:585)
II	+ adjuv. chemo if ↑ risk: tumor >2 cm *or* ⊕ LN *or* triple ⊖ *or* Oncotype DX-guided + hormonal Rx for ER/PR ⊕: add ovarian suppression if ↑ risk (*NEJM* 2018;379:122) + anti-*HER2* Rx and chemo if *HER2* ⊕ and tumor ≥1 cm or ⊕ LN
III	Neoadjuvant chemo → surgery + RT ± adjuvant chemotherapy + hormonal Rx for ER/PR ⊕: add ovarian suppression if premenopausal + anti-*HER2* Rx for *HER2* ⊕: usually trastuzumab + pertuzumab
IV	ER/PR ⊕: combined aromatase & CDK4/6 inhibitors (*NEJM* 2016;375:1925) ER/PR ⊖/*HER2* ⊕: chemo + anti-*HER2* therapy Triple ⊖: chemo ± immune checkpoint inhibitor Bony mets: bisphosphonates & denosumab ↓ fractures (*Cochrane* 2017;CD003474)

Surgery and Radiation for Local Control	
Intervention	**Indication**
Breast conserving	Stage I–II, lumpectomy + sentinel lymph node biopsy* + RT
Modified radical mastectomy	Large tumor relative to breast, multicentric dis., prior chest RT, diffuse microcalcifications, ⊕ margins after lumpectomy
Post-mastectomy Radiation	≥4 ⊕ LN, tumor >5 cm, ⊕ surgical margins, chest wall or skin involvement (*Lancet* 2014;384:1848)

*Axillary lymph node dissection indicated for palpable axillary LNs

Systemic Therapy		
Indic.	**Class**	**Examples**
ER/PR ⊕ (*Lancet* 2017;389:2403)	Endo (*NEJM* 2019;380:1226)	**Tamoxifen:** adjuvant Rx for low-risk pre-meno; ↓ recurrence & ↓ mortality; 10 y superior to 5 y (*Lancet* 2011;378:771 & 2013;381:805) **Aromatase inhib** (AI; anastrozole, letrozole, exemestane): adjuvant Rx for post-meno; ↑ OS vs. tam. (*Lancet* 2015;386:1341); 7 y of Rx ↑ DFS vs. 5 y of Rx (*NEJM* 2021;385:395) Adding selective ER degrader (fulvestrant) to AI ↑ OS if mets
	Ovarian suppress.	**LHRH agonists** (eg, leuprolide) or oophorectomy: adjuvant Rx for high-risk pre-meno combined with tam. or AI (*NEJM* 2018;379:122)
	Cell prolif. (*NEJM* 2012;366:520)	**CDK4/6 inhib** (eg, palbociclib, ribociclib): in early stage, ↑ IDFS when added to AI; in stage IV, ↑ PFS or OS when added to AI or fulvestrant (*NEJM* 2018;379:1926 & 2024;390:1080) **mTOR inhib** (everolimus): + AI (exemestane) ↑ OS in stage IV
PIK3CA ⊕	PI3K inhib	Addition of **alpelisib** or **inavolisib** ↑ PFS in met HR ⊕ (*NEJM* 2019;380:1929 & 2024;391:1584)
AKT1 or PTEN mut.	AKT inhib	Capivasertib + fulvestrant ↑ PFS in met HR ⊕ (*NEJM* 2023;388:2058)
HER2 ⊕ (*Lancet* 2017;389:2415)	HER2-targeted	**Trastuzumab** + **pertuzumab** (anti-HER2): 1st-line Rx combined w/ chemo (*NEJM* 2015;372:724 & 2025;392:249) **Trastuzumab deruxtecan** (mAb linked to chemo): 2nd line for met

		disease, ↓ risk disease progression vs. trastuzumab emtansine, ↑ lung toxicity (*NEJM* 2024;391:2110) Tucatinib + trastuzumab + capecitabine: 3rd line, esp if CNS mets **Trastuzumab emtansine** (mAb linked to chemo): ↓ recurrence and death if residual disease post neoadj. Rx (*NEJM* 2019;380:617)
Stage I–III (above)	Chemo	**Neoadjuvant:** to conserve breast & evaluate Rx efficacy, equivalent OS as adjuvant (*JCO* 2008;26:778) **Adjuvant:** use anthracycline ± taxane. Nb, endocrine only for some ER/PR ⊕ based on oncotype Dx (see staging).
Triple ⊖	Immune	**Pembrolizumab** (anti-PD-1 mAb) + chemo 1st line for early stage (*NEJM* 2024;391:1981) & PD-L1 ⊕ met dis. (*Lancet* 2020;396:1817)
	Ab-drug conjugate	**Sacituzumab govitecan**: anti-TROP2 Ab linked to chemo ↑ PFS & OS in heavily pre-Rx'd metastatic disease (*Lancet* 2023;402:1423)
BRCA ⊕	PARP inh	**Olaparib & talazoparib** (*NEJM* 2017;377:523 & 2018;379:753)

DFS, dis.-free survival; IDFS, invasive dis.-free survival; OS, overall survival; PFS, progression-free survival

PROSTATE CANCER

Epidemiology and risk factors (*JAMA* 2025;333:1433)

- Most common cancer in U.S. men; 2nd most common cause of cancer death in men
- Lifetime risk of prostate cancer dx ~16%; lifetime risk of dying of prostate cancer ~3%
- ↑ risk with ↑ age (rare if <45 y), in African Americans, ⊕ FHx, BRCA mutations

Clinical manifestations

- Most prostate cancers (78%) are asymptomatic and localized at diagnosis
- Metastatic dis. sx primarily from bone mets: bone pain, spinal cord compression, cytopenias

Screening (*JAMA* 2014;311:1143; *Lancet* 2014;384:2027)

- **PSA:** 4 ng/mL cut point neither Se nor Sp; can ↑ with BPH, prostatitis, acute retention, after bx or TURP, and ejaculation (*no significant ↑ after DRE, cystoscopy*); 15% of men >62 y w/ PSA <4 & nl DRE have bx-proven T1 cancer (*NEJM* 2004;350:2239)
- Digital rectal exam no longer recommended due to limitations, no mortality benefit
- ACS rec: ≥50 y (or ≥45 y AA or ⊕ FHx) discuss PSA screening, informed decision making
- USPSTF (*JAMA* 2018;319:1901) rec discuss pros/cons w/ Pt (no ↓ in prostate ca-related mort.)

Diagnostic evaluation, staging, and treatment

- **Transrectal ultrasound** (TRUS)-**guided biopsy** (6–12 cores)
- Multiparametric MRI (± endorectal coil): ↑ detection & ↓ unneeded bx (*NEJM* 2024;391:1083)
- **Gleason score & grade group (histology):** Gleason score determines Grade Group. 1 = best → 5 = worst. Group 1: 3+3=6 (most common histologic pattern is 1st #, next is 2nd #), Group 2: 3+4=7, Group 3: 4+3=7, Group 4: 4+4=8, Group 5: all higher.

Risk Stratification & Treatment of Localized Prostate Cancer (*JAMA* 2017;317:2532)				
Risk	**T Stage**	**Gleason Score & Path**	**Imaging**	**Treatment**
Very low*	T1c	Grade Group 1, <3 cores ⊕, <50% ⊕ in any core, *and* PSA <10 ng/mL & density <0.15 ng/mL/g	Not Indic.	Consider active surveill. if very low risk (2× mets but ≈ mort.; *NEJM* 2023;388:1547), *or* EBRT (external beam RT), *or* Radical prostatectomy (RP) RP vs. EBRT based on Pt, long-term tox† of Rx
Low*	T1–2a	Grade Group 1, *and* PSA <10 ng/mL		
Intermed*	T2b–T2c	Grade groups 2–3, *or* PSA 10–20 ng/mL	Bone scan & CT A/P	RP *or* EBRT+ADT (4–6 mo)
High Very high	T3a–T4	Grade Groups 4–5, *or* PSA >20 ng/mL		EBRT+ADT (18–36 mo) *or* EBRT+ADT+abiraterone

*In asx Pts w/ life expect ≤5 y & very low-to-intermed risk dis., no w/up or Rx until sx.

†RP more short-term impotence (unless ADT) & incont than RT; over yrs → similar (*NEJM* 2016;375:1425)

Evaluation and Treatment of Metastatic Prostate Cancer	
Androgen deprivation therapy (ADT)	Prostate ca requires androgen signaling for growth. ADT backbone of Rx. Med: 1. Luteinizing hormone–releasing hormone (LHRH) agonist (eg, leuprolide) ± 1st-gen anti-androgen (nilutamide, bicalutamide), *or* 2. LHRH antagonist (degarelix) Surgery: bilateral orchiectomy
Hormone-sensitive prostate cancer (HSPC)	**Def:** ADT sensitive (ie, PSA ↓ w/ Rx): all prostate ca initially sensitive **Workup/testing:** PEx & PSA q3–6mos; sx-guided imaging **Rx:** 1. ADT alone (only if minimal disease, eg, rising PSA); *or* 2. ADT + abiraterone/pred or enza/apalutamide (↑ OS vs. ADT alone); *or* 3. Docetaxel + ADT + abiraterone/pred (↑ OS vs. w/o abiraterone/pred), espec. in high-volume disease (*Lancet* 2022;399:1695) + RT ↑ PFS but not OS in low-volume disease (*Lancet* 2024;404:2065)
Castration-resistant prostate cancer (CRPC) *Always continue ADT*	**Def:** All met. HSPC eventually becomes CRPC (ie, progression despite castration androgen levels on ADT), due to re-estab. of androgen signaling via other mech or hist tx to neuroendocrine (*JCO* 2018;36:2492) **Rx:** New-gen. anti-androgens: abiraterone (biosynth inhib.) + pred, or enza/daro/apalutamide (androgen receptor blockers) ↑ PFS & OS **Targeted:** *BRCA1/2, ATM* (homologous recomb genes, ~20%): olaparib; *MSI-H*/Lynch syndrome (2–5%): pembro; *Cancer vaccine:* Sipuleucel-T **Chemo:** doce/cabazitaxel +pred/dex+Lutetium-177 (*NEJM* 2021;385:1091) **Bone-active agents:** 1. denosumab or zoledronic acid ↓ skeletal-related events (SREs); 2. radium-223 used in bone-only dis, ↓ SREs & ↑ OS

(*NEJM* 2017;377:338 & 352; 2019;381:121; 2019;381:13; 2023;389:1453; *Lancet* 2016;387:1163)

Prognosis and monitoring

- PSA level, Gleason score/grade group and age are predictors of metastatic disease
- In surgically treated Pts, 5-y relapse-free survival >90% (excellent) if disease confined to organ, ~75% if extension through capsule, and ~40% if seminal vesicle invasion
  PSA q6mo for 5 y if curative Rx; consider PET Axumin scan if ↑ PSA ± equivocal bone scan

COLORECTAL CANCER (CRC)

Epidemiology and risk factors (*CA Cancer J Clin* 2023;73:17)

- 3rd most common cancer in U.S. men & women; 2nd leading cause of all cancer death
- 90% of cases occur after age 50. ~75% are sporadic.
- IBD a/w ~0.3%/y ↑ risk of CRC. ↑ risk w/ ↑ extent and duration of disease.

Heritable Genetic Syndromes			
Disorder	**CRC risk**	**Pathophysiology**	**Assoc Cancers**
Hereditary nonpolyposis colorectal cancer (HNPCC or Lynch)	~80% lifetime	Most common hered. CRC (~3%). Mismatch repair mut (eg, *MSH2*, *MLH1*). Dx: ≥3 family HNPCC cancer, 1 dx before 50 y, involves 2 gen. Typically **right-sided**.	**Endometrial**, ovarian, stomach, urothelial, small bowel, & pancreas
Familial adeno polyposis (FAP)	100% lifetime	Mutation in *APC* gene → 1000s of polyps at young age	Thyroid, stomach, small bowel
MUTYH-assoc. polyposis (MAP)	40–100% lifetime	Autosomal *recessive;* consider if mult. polyps but ⊖ for FAP	Duodenal, ovarian, bladder, skin

- ASA rec for 1° prev. if 50–59 y & ≥10% 10-y CRC risk. Must take for at least 10 years.

Screening (*JAMA* 2021;325:1965)

- *Average-risk Pts*: start at age 45, repeat q1–10y based on screening modality
- ↑ *risk Pts*: ⊕ FHx: screen age 40 or 10 y before index dx, then q5y. IBD: colo 8–10 y after dx, then q1–2y. Suspect familial syndrome: genetic counsel, screen age 20–25, yearly.
- **Colonoscopy:** *preferred*; 90% Se for lesions >1 cm. ↓ CRC (*NEJM* 2022;387:1547). If polyp, re ✓ in 3–5 y. Adenomatous polyp removal a/w ↓ CRC mortality (*NEJM* 2012;366:687). *Adenoma*: ↑ risk of malig. if >2.5 cm, villous, or sessile.
- **Sigmoidoscopy:** benefit w/ 1-time flex-sig (*Lancet* 2017;389:1299); less Se than colo or CTC
- **CT colonography (CTC):** ~90% Se for lesions ≥1 cm but less if smaller (*NEJM* 2008;359:1207). If high risk, Se only 85% for neoplasia ≥6 mm (*JAMA* 2009;301:2453).
- **Combo DNA** + **Hb immunoassay** w/ ~90% Se & Sp (*NEJM* 2024;390:984)
- Occult blood (FOBT): use 3-card home testing (Se 24%) yearly

Clinical manifestations

- Distal colon: Δ **bowel habits/caliber**, **obstruction**, colicky abd. pain, **hematochezia**
- Proximal colon: **iron defic. anemia**, dull vague abd pain, liquid stool

Cancer genetics (*Nature* 2014;513:382)

- **Microsatellite stable (MSS) vs. high instability (MSI-H):** latter sign of mismatch repair gene failure, accounts for 15% CRC, presents more often as early stage, ~5% of met dis.
- **Mutations:** *APC* (~80%); *KRAS* (~40%); *TP53* (50–70%); *DCC*, *SMAD4*, *BRAF* (~15%), *HER2* amplification (<5%)

Staging and treatment

- TNM staging, including CT chest and abdomen/pelvis with contrast ± MRI pelvis for rectal

- Baseline **CEA**: monitor postresection or follow response; *not* for screening
- **Chemo options**: 5-FU/leucovorin + oxaliplatin &/or irinotecan (FOLFOX, FOLFIRI, FOLFOXIRI, resp). Capecitabine oral 5-FU prodrug. *Anti-VEGF* (bevacizumab) added to chemo ↑ OS in met CRC (*NEJM* 2004;350:2335 & 2023;388:1657390). Trifluridine + tipiracil (FTD-TPI) in progressive disease (*NEJM* 2015;372:1909).
- **Targeted therapy:** anti-EGFR mAb (cetuximab, panitumumab) (*NEJM* 2013;369:1023) *BRAF* V600E: encorafenib+binimetinib+cetuximab (*NEJM* 2019;381:1632) HER2+: T-DXd or trastuzumab+pertuzumab, lapatinib, or tucatinib (*Lancet* 2016;17:738) KRAS G12C: RASi (sotorasib, adagrasib)+anti-EGFR mAb (*NEJM* 2023;388:44 & 389:2125)
- **ImmunoRx** (ICI): in MMRd/MSI-H or POLE/POLD1 locally adv. or met CRC (*NEJM* 2024;390:1949 & 391:2014); dostarlimab for loc. adv. MMRd rectal cancer (*NEJM* 2022;386:2362)
- **Radiation:** loc. adv. rectal (T3/N+) & colon (unresectable); consider for oligo-mets

TNM	Path. Criteria	5-Y Surv.	Treatment
I	Submucosa/muscularis	94–97%	Surgery alone (resect & analyze ≥12 LN)
IIA	Serosa	83%	Surgery ± Chemo for high-risk (obstruction, perf, adherence, inadequate LN sampling)
IIB	Peritoneum	74%	
IIC	Direct invasion	56%	
IIIA	≤6 ⊕ LNs	86%	Surgery + FOLFOX (6 mo) or CAPOX (3–6 mo) (*NEJM* 2018;378:13) Pre RT ± chemo if rectal (*NEJM* 2006;355:1114)
IIIB	Varying # ⊕ LNs & local invasion	51–77%	
IIIC		15–47%	
IV	Distant metastases* (*NEJM* 2014;371:1609)	5%	Chemo (FOLFOXIRI if high-risk) ± anti-PD-1 (MSI-H only) ± resect isolated mets

*Oligometastatic dis (few, limited mets) sometimes still curable w/ chemo + metastasectomy/radiation

PANCREATIC TUMORS

Genetics and path (*Nat Rev Dis Primers* 2016;2:16022)

- Histologic types: **adenocarcinoma** (~85%), acinar cell carcinoma, endocrine tumors, cystic neoplasms (<10%); rarely, mets to pancreas (eg, lung, breast, renal cell)
- Location: ~60% in head, 15% in body, 5% in tail; in 20% diffuse infiltration of pancreas
- Adeno. mut.: *KRAS* (>90%), *p16* (80–95%), *p53* (50–75%), *SMAD4* (~55%), *BRCA* (10%)

Epidemiology and risk factors (*Lancet* 2016;388:73)

- 4th leading cause of cancer death in U.S.; 80% panc adeno in ages 60–80 y; M>F (1.3:1)
- Acquired risk factors: **smoking** (RR ~1.5; 25% cases), obesity, chronic pancreatitis, T2DM
- Hereditary (5–10%): familial breast/ovarian CA (*BRCA2*); *hereditary chronic pancreatitis* (mutation in cationic trypsinogen gene (*PRSS1*, *SPINK1*)); *familial cancer syndromes:* atypical multiple mole melanoma (*CDKN2A/p16*), Peutz–Jeghers (*LKB1*), ataxia-telang.

Clinical manifestations

- **Painless jaundice** (w/ pancreatic head mass), **pain** radiates to back, ↓ **weight** & appetite
- New-onset atypical DM (25%); migratory thrombophlebitis (Trousseau's syndrome)
- Exam: jaundice, RUQ/epigastric nontender mass, palpable gallbladder (Courvoisier's sign); hepatomegaly; ascites; L supraclavicular node (Virchow's)
- Laboratory tests may show ↑ bilirubin, ↑ alk phos, anemia

Diagnostic and staging evaluation

- **Pancreatic protocol CT scan** (I^+ w/ arterial & venous phase imaging) or **MRI w/ contrast**
- *If no lesion seen but concerning signs & sx as above* → EUS, ERCP, or MRCP
- **Biopsy pancreatic lesion** via EUS-guided FNA (pref. for surgical candidates) or CT- guided (risk of seeding); if possible metastases, biopsy those for staging *and* dx.
- ✓ **CA19-9** pre-op (nb, can be ↑ in benign liver/biliary dis.); may be useful to trend post-op
- **Germline genetic testing** for all Pts with pancreatic cancer

Clinical (Radiologic) Staging Pancreatic Adenocarcinoma	
Resectable	No extrapanc. dis. or bulky LAN; no **arterial** tumor contact [celiac axis (CA), SMA, common hepatic (CHA)]; and no **venous** contact [SMV, portal vein (PV)] or ≤180° + patent veins (ie, no tumor thrombus)
Borderline resectable	No extrapanc dis. or bulky LAN. **Head/uncinate:** contact w/ CHA (no extension to CA or HA bifurcation), SMA contact ≤180°, variant anatomy. **Body/tail:** contact CA ≤180° or >180° but w/o gastroduodenal art. or aortic. **Venous:** SMV & PV contact ≤180° w/ contour irreg; contact w/ IVC.
Unresect.	**Distant mets**; or **head/uncinate:** contact >180° SMA, CA; or **Body/tail:** contact >180° SMA or CA; CA & aortic involvement; or **Venous:** SMV/PV involvement/not reconstructible

Treatment of pancreatic adenocarcinoma (*Lancet* 2016;388:73)

- **Resectable:** pancreaticoduodenectomy (**Whipple procedure**) + adjuvant chemo: modified FOLFIRINOX (5-FU + leucovorin, irinotecan, oxaliplatin) if ECOG 0–1 (*NEJM* 2018;379:2395), o/w gemcitabine + capecitabine (*Lancet* 2017;389:1011). Gemcitabine monoRx recently standard, but now w/ ↓ role. Role of RT is controversial.
- **Borderline:** goal to ↓ tumor to allow complete resection (R0—neg margin at histology) using neoadjuvant Rx (various approaches tested). General schema: **chemo ± RT → restage & potential resection** depending on response. May need vasc. reconstruction during resection. Regimens include: FOLFIRINOX; gemcitabine + nab-paclitaxel.
- **Locally advanced** (ie, unresectable): Rx is typically palliative. However, in highly select Pts recent trend toward Rx w/ FOLFIRINOX plus XRT followed by laparotomy for response assessment (imaging can be unreliable) and potential resection.
- **Metastatic:** *clinical trials preferred;* Rx based on performance status (PS)
  - *Good PS:* **FOLFIRINOX** (*NEJM* 2011;364:1817); **gemcitabine** + **nab-paclitaxel** (*NEJM* 2013;369:1691); germline *BRCA1/2* mut: maintenance olaparib (*NEJM* 2019;381:317) also ↑ response to platinum combo chemo (eg, cisplatin w/ gemcitabine), ICI for MSI-high
  - *Poor PS:* gemcitabine; capecitabine; continuous infusion 5-FU
- **Palliative care:** *Biliary/gastric outlet obstruct*.: endoscopic stenting, IR drain, surg bypass. *Pain:* opiates, celiac plexus neurolysis, XRT. *Wt loss:* enzyme replacement.

Prognosis

- Resectable: if Rx'd w/ adjuvant FOLFIRINOX, 50+ mos, o/w ~30 mos
- Unresectable: if locally advanced ~1–2 y; if metastatic, ~1 y

Cystic lesions of the pancreas (*Am J Gastroenterol* 2018;113:464)

- **Serous cystadenoma:** usually benign; central scar or honeycomb appearance on imaging
- **Mucinous cystic neoplasm** (MCN): predominantly young females; multiloculated tumors in body or tail w/ ovarian-type stroma and mucin-rich fluid w/ ↑ CEA levels; precancerous
- **Intraductal papillary mucinous neoplasm** (IPMN): arises in main panc duct or branch

OTHER SOLID TUMORS

Hepatocellular Carcinoma (HCC)

Risk factors (globally, 3rd leading cause of cancer death, espec. in Africa & Asia)

- **Cirrhosis:** present in 70–90% HCC cases
- **Infectious:** HCV & HBV (~75%), HBV/HDV coinfection; HBV can cause HCC w/o cirrhosis
- **Toxic:** EtOH (cases in U.S.), tobacco, aflatoxin from *Aspergillus*
- **Metabolic disorders:** NASH, DM, autoimmune hepatitis, hemochromatosis

Screening (screen high-risk Pts: cirrhosis, chronic HBV)

- **Ultrasonography** (U/S) + AFP q6mos; if high risk may alternate U/S w/ **MRI**
- If lesion found or increasing AFP, perform **3-phase contrast CT** or **MRI**

Clinical manifestations

- Exam: nonspec. c/w liver dysfxn (eg, hepatomegaly, ascites, jaundice, encephalopathy)
- Labs: coagulopathy, low albumin, elevated LFTs; r/o other etiologies of liver dysfxn

Diagnosis

- **Can diagnose w/o biopsy in high-risk Pts with 3-phase contrast CT** or **MRI**
- Only 15% of liver masses are HCC; liver metastases from other 1° more common

Treatment (*Lancet* 2024;400:1345)

- Localized disease (goal = cure) → **resection** if feasible (preferred), ablation, transarterial chemoembolization, or radiotherapy (SBRT) also options. Inadequate hepatic reserve → **liver transplant** if able (*NEJM* 1996;334:693); nonsurgical local and/or systemic Rx if not.
- Systemic Rx: atezolizumab (anti-PD-L1) + bevacizumab preferred (*NEJM* 2020;382:1894), 2nd line: kinase (lenvatinib, sorafenib) or PD-(L)1 inhib (*Lancet* 2017;389:2492 & 2018;391:1163)

Gastric/Esophageal Cancer

Epidemiology (*Lancet* 2017;390:2383 & 2020;29:635)

- **Esophageal:** Predominantly adenocarcinoma in U.S. (>60%), squamous cell (SCC) more common globally. Risk factors: GERD → Barrett's esoph (adeno), smoking/EtOH (SCC).
- **Gastric:** Predominantly adenocarcinoma. Risk factors include *H. pylori*, FHx & cancer syndromes (eg, Lynch syndrome [MMRd], Hereditary Diffuse Gastric Cancer [CDH1/CTNNA1-altered]), nitrosamines in diet, smoking/EtOH.

Screening

- **Esophageal:** screen for Barrett's w/ endoscopy if multiple risk factors (eg, hiatal hernia, age ≥50, male, chronic GERD, obese, smoking, FHx). Repeat q3–5y if Barrett's.
- **Gastric:** typically not screened in U.S. More common in regions w/ higher incidence (eg, Japan, Korea, Chile) w/ endoscopy or barium radiographs.

Clinical manifestations

- Dysphagia, wt loss, early satiety, nausea, typically occult GI bleed, vague abd discomfort
- Exam: diffuse seborrheic keratoses (Leser–Trélat sign, though nonspecific)

Diagnosis and staging

- Both diagnosed w/ **endoscopic biopsy**. CT chest/abd/pelvis for staging. If no mets → PET/CT (occult mets). If neg → endoscopic ultrasound for locoregional assessment.
- Staging laparoscopy needed for gastric cancer
- Molecular: ✓ HER2, PD-L1, microsatellite instability & mismatch repair

Treatment

- If localized disease and good performance status/fit, goal is cure with surgery
- **Localized**: resection. Periop or neoadjuvant chemo/chemoRT if stage IB or higher (*NEJM* 2012;366:2074). Adjuvant nivolumab (*NEJM* 2021;384:1191).
- **Advanced**: 1st line: chemo w/ platinum/fluoropyrimidine. Add trastuzumab if HER2⊕ (*Lancet* 2010;376:687), nivolumab if PD-L1⊕ (*Lancet* 2021;398:27), or trastuzumab/pembro if both (*Lancet* 2023;402:2197). 2nd line: ramucirumab (VEGFi) + paclitaxel (*Lancet* 2014;15:1224), nivolumab/pembrolizumab.
- **Supportive care**: pain/nausea mgmt. Consider G/G-J tube if obstruction, IVF prn.

Cutaneous Melanoma

Clinical presentation and workup

- Suspicious skin lesion (ABCDE: asymm, border, color, diameter >6 mm, evolution) → bx
- **Staging:** I & II = no regional/distant mets. III = regional LN ⊕ or in-transit/satellite mets. Ulceration & thickness confer substage within I–III. IV = distant mets.
- **Prognosis:** excellent if localized dis., ≤1 mm thickness. Varies widely stage IIIA–IIID based on nodal burden (5 yr OS 20–70%; ulceration, mitotic rate, & invasion depth predictive).
- Molecular diagnostics: check for BRAF V600E (present in ~50% of melanomas)

Treatment (*NEJM* 2021;384:2229)

- Wide surgical excision + sentinel node mapping (unless *in situ* or low risk of node ⊕)
- If sentinel node ⊕, nodal dissection vs. observation. No difference in survival w/ observation (*Lancet Oncol* 2016;17:757; *NEJM* 2017;376:2211).
- **Immune checkpoint inhibitors** (qv) (ICI): pembro, nivo, nivo/ipi, nivo/rela
- ***BRAF/MEK* inhib.** (eg, vemurafenib/trametinib) if activating *BRAF V600E* mutation present
- Adjuvant for high-risk node ⊕ disease: ICI (↑ RFS, *Lancet Onc* 2020;21:1465; *JCO* 2020;38:3925) or dabrafenib/trametinib (BRAF ⊕, ↑ OS, *NEJM* 2024;391:1709)
- Neoadj. nivo/ipi ↑ event-free survival vs. adj. nivo in resectable stage III (*NEJM* 2024;391:1696)
- Metastatic: ICI mono vs. dual (ipi+nivo a/w improved response rate especially for intracranial mets, *NEJM* 2018;379:722). Consider targeted Rx if BRAF ⊕. Tumor-infiltrating lymphocyte therapy (TIL), eg, lifileucel, for 2nd line.

Ovarian Cancer

Histopathology

- Epithelial ovarian carcinoma (EOC, 95%): high-grade serous (most common, often dx at late stage, poor prognosis), low-grade serous, endometrioid, clear cell, mucinous
- Nonepithelial (~5%): germ cell, sex cord-stromal. Rare: small cell, sarcoma.

Risk factors for EOC (*Nat Rev Dis Primers* 2016;2:16061)

- Nulliparity, early menarche, late menopause; EOC risk ↑ 2–7% each additional ovulatory yr
- **Genetics:** germline testing/genetics referral for all Pts (25% w/ heritable mutation), can inform Rx (eg, PARPi maintenance, *JCO* 2020;38:1222). 5% risk if one 1st-degree relative w/ ovarian cancer, 3.5% risk if one 2nd-degree relative (*Obstet Gynecol* 1992;80:700). ↑↑ risk w/ hereditary syndromes: *BRCA1/2* (lifetime risk 17%/44%), Lynch syndrome (non-serous).
- History of pelvic radiation, endometriosis, or obesity (risk association less clear)

Clinical manifestations

- Nonspecific history of bloating, pelvic/abdominal pain, bowel sx, urinary sx
- Exam may reveal palpable pelvic mass, abdominal distention, or ascites

Diagnosis

- No screening modalities have shown survival benefit; no data to support at this time
- If concerning signs/sx, obtain pelvic U/S and/or CT A/P or pelvic MRI, CA-125
- Pathologic dx based on biopsy of lesion or sampling of ascitic fluid

Treatment

- Cytoreductive surgery: survival benefit even for stage IV and relapsed disease (*Gynecol Oncol* 2013;130:493; *NEJM* 2021;385:2123). Consider neoadj. chemo to ↑ likelihood of maximal cytoreduction at surgery and reduce surgical morbidity.
- Chemo: 1st line (neoadj., adj., adv.): carboplatin+paclitaxel (CP). PARPi maintenance (olaparib, niraparib, rucaparib; esp if homologous recombination deficient [eg, *BRCA1/2*]) or bevacizumab maintenance if homologous recombination proficient.
- Recurrence at >6 mos = **platinum sensitive** → Rx w/ platinum doublet. If <6 mos = **platinum resistant** → single-agent chemo (eg, liposomal doxorubicin, gemcitabine) ± bevacizumab.

Primary CNS Tumors and Brain Metastases

Presentation and diagnosis

- Suspect if new focal neurologic deficits, seizure, memory or balance issues, or evidence of ↑ intracranial pressure (HA, n/v, vision change)
- **MRI brain** for suspected CNS tumors; CT less Se. Consider LP if c/f CNS lymphoma.

Primary CNS tumors

- **Meningioma:** histopath. grading (WHO grades). Grade 1 = benign, asx/small → observe. Large or sx → resection if able, radiation if not. Grade 2–3 → resection + adjuvant RT (defer if risk of RT complication high and tumor totally resected).
- **Glioma:** histopath. grading, Grade 1/2/3: astrocytoma, oligodendroglioma most common; Grade 4: glioblastoma. Grade 3/4 = "high grade" (*Neuro Oncol* 2021;23:1231).
- Notable testing: 1p/19q, *IDH*, *MGMT* methylation (predicts sensitivity to temozolomide)
- Treatment: **max resection as feasible** → adjuvant RT + temozolomide → surveillance. Steroids if neuro sx, hold until biopsy if c/f 1° CNS lymphoma. Anti-epileptics if seizures.

- Prognosis based on grade & histology. For glioblastoma, overall survival 12–15 mos, based on extent of tumor resection (*J Neurosurg* 2014;120:31).

Metastatic CNS lesions

- More common than 1°. Most common: lung, breast, melanoma, RCC, gastro-esoph.
- **Surgery** if oligomet disease or symptomatic & resectable, steroids if neuro sx
- **Radiation** particularly if multiple mets or inoperable. Consider WBRT if many mets.
- Some systemic therapies (checkpoint inhibitors, targeted Rx in NSCLC) have CNS activity

ONCOLOGIC EMERGENCIES

Fever and Neutropenia (FN)

Definition

- Fever: single oral temp ≥38.3°C (101°F) or ≥38°C (100.4°F) for ≥1 h
- **Neutropenia:** ANC <500 cells/µL or <1000 cells/µL with predicted nadir <500 cells/µL

Pathophysiology and microbiology

- Predisposing factors: catheters, skin breakdown, GI mucositis, obstruction (lymphatics, biliary tract, GI, urinary tract), immune defect associated with malignancy
- Often thought due to seeding of bloodstream by GI flora, eg, GNRs (esp. *P. aeruginosa*)
- Neutropenic enterocolitis (typhlitis): RLQ pain, watery/bloody diarrhea, cecal wall thickening
- Gram ⊕ infections have recently become more common (60–70% of identified organisms)
- Fungal superinfection often results from prolonged neutropenia & antibiotic use

Prevention (only if intermediate or high risk)

- Bacterial: consider FQ if neutropenic esp steroids+ALL; ↓ mortality (*Cochrane* 2012;CD004386)
- Fungal: consider during neutropenia in blood cancers (posa/fluconazole, micafungin)
- Viral: consider during active Rx in blood cancers (acyclovir, famciclovir, valacyclovir)

Role of hematopoietic growth factors

- Granulocyte (G-CSF) and granulocyte-macrophage (GM-CSF) colony-stimulating factors can be used (*but not in AML*) as 1° Ppx when expected FN incidence >20% or as 2° Ppx after FN has occurred in a prior cycle (to maintain dose-intensity for curable tumors)
- CSFs ↓ rate of FN but have not been shown to affect mortality (*Cochrane* 2014;CD003039)

Diagnostic evaluation

- Exam: skin, oropharynx, lung, perirectal area, surgical & catheter sites; *avoid rectal exam*
- Studies: U/A, blood (periph & through each indwelling catheter port), urine, & sputum cx; for localizing s/s → ✓ stool (*C. diff*, cx), peritoneal fluid, CSF (rare source)
- Imaging: CXR; for localizing s/s → CNS, sinus, chest or abdomen/pelvis CT
- Caveats: neutropenia → impaired inflammatory response → *exam and radiographic findings may be subtle;* absence of neutrophils by Gram stain does *not* r/o infection

Risk stratification (factors that predict lower risk)

- Hx: outPt, ECOG 0/1, <60 y, solid tumor, no sx, no major comorbidities, no h/o fungal infxn
- Exam: temp <39°C, no tachypnea, no HoTN, no ΔMS, no dehydration
- Labs: ANC >100 cells/μL, anticipated duration of neutropenia ≤100 cells/μL <7 d

Antibiotic therapy

- Empiric regimens should include **antipseudomonal activity**; consider VRE coverage if ⊕
- **Low risk:** PO abx or home IV abx may be considered in select Pts (*JCO* 2013;31:1149)
  PO options: cipro+amoxicillin-clavulanate; levofloxacin; moxifloxacin (avoid if FQ Ppx)
- **High risk: hospital admission & IV abx;** *monotherapy preferred*
  options: **cefepime**, imipenem, meropenem, piperacillin/tazobactam, ceftazidime
- Antifungal Rx added for neutropenic fever ≥4 d despite abx: **micafungin**, liposomal amphotericin B, caspofungin, anidulafungin, voriconazole, & posaconazole are options
- **Vancomycin** *only if* HoTN, PNA, clinically apparent catheter-related or soft-tissue infxn, gram ⊕ BCx, mucositis + on quinolone Ppx; d/c when BCx ⊖ × 48 h for GPCs

Duration of therapy

- Known source: complete standard course (eg, 14 d for bacteremia)
- Unknown source: continue antibiotics until afebrile *and* ANC >500 cells/μL
- Less clear when to d/c abx when Pt is afebrile but prolonged neutropenia

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Metastatic Spinal Cord Compression

Clinical manifestations (*Lancet Neuro* 2008;7:459)

- Metastases located in vertebral body extend and cause epidural spinal cord compression
- **Prostate**, **breast**, and **lung** cancers are most common, followed by RCC, NHL, myeloma
- **Site of involvement: thoracic** (60%), lumbar (25%), cervical (15%)
- Signs and symptoms: pain (>95%, precedes neuro Δs), weakness, autonomic dysfunction (urinary retention, ↓ anal sphincter tone), sensory loss

Diagnostic evaluation

- Always take back pain in Pts w/ cancer seriously. Urgent **whole-spine MRI**; CT if unable.
- **Do *not* wait for neurologic signs to develop** before initiating evaluation b/c duration & severity of neuro dysfxn before treatment are best predictors of neurologic outcome

Treatment (*NEJM* 2017;376:1358)

- **Dexamethasone** (10 mg IV × 1 STAT, then 4 mg IV or PO q6h) *initiate immediately* while awaiting imaging if back pain + neurologic deficits
- Emergent RT or surgical decompression if confirmed compression/neuro deficits
- Surgery + RT superior to RT alone for neuro recovery in solid tumors (*Lancet* 2005;366:643)
- If pathologic fracture causing compression → surgery; if not surgical candidate → RT

Tumor Lysis Syndrome

Clinical manifestations (*NEJM* 2011;364:1844)

- Large tumor burden or a rapidly proliferating tumor → spontaneous or chemotherapy- induced release of intracellular electrolytes and nucleic acids
- Most common w/ treatment of **high-grade lymphomas** (**Burkitt's**) and **leukemias** (**ALL**, **AML**, **CML in blast crisis**). *Very rare w/ solid tumors*; rarely due to spont. necrosis.
- Electrolyte abnormalities: ↑ K, ↑ uric acid, ↑ PO_4 → ↓ Ca; **renal failure** (urate nephropathy)

Prophylaxis

- Allopurinol 300 mg qd to bid PO or 200–400 mg/m^2 IV (adjusted for renal fxn) & aggressive hydration prior to beginning chemotherapy or RT

Treatment

- *Avoid* IV contrast and NSAIDs; treat hyperK, hyperPO_4, and only *symptomatic* hypoCa
- Allopurinol + aggressive IV hydration ± diuretics to ↑ UOP for goal 80–100 mL/h
- Rasburicase (0.1–0.2 mg/kg or 6 mg IV fixed dose) for ↑↑ uric acid esp. in aggressive malig (*JCO* 2003;21:4402; *Acta Haem* 2006;115:35). ***Avoid in G6PD def*** (hemolytic anemia). Consider G6PD testing in Jehovah's Witnesses especially if Black (12% prevalence).
- Hemodialysis may be necessary; early renal consultation for renal insufficiency or ARF

THERAPY SIDE EFFECTS

Nausea & vomiting common (*NEJM* 2016;374:1356; 375:134 & 177)

Select Adverse Effects from Cancer-Directed Therapies*		
Toxicity	**Common Agents**	**Comments**
Cardiotoxicity (*NEJM* 2016;375:1457)	**Anthracyclines**	Dose-dependent CMP; ✓ EF pre-Rx
	5-FU	Spasm → ischemia; CCB may prevent
	Trastuzumab	CMP, esp w/ anthracycline, TTEs for EF
	Tyrosine kinase inhib (TKI)	QTc prolongation, CMP, angina
	Cyclophosphamide	Myopericarditis (esp. in BMT)
	Cisplatin	AKI → HypoMg/HyperK → arrhythmia
Pulmonary (*Sem Oncol* 2006;33:98)	Busulfan	~8% fibrosis or DAH; if severe → steroids
	Bleomycin	~10% IPF; ✓ PFTs pre-Rx; Rx: steroids
	TKI	Pneumonitis, pleural eff. (esp. dasatinib)
	Cyclophosphamide	Pneumonitis, progressive fibrosis; Rx: d/c
	Bevacizumab	Pulm. hemorrhage (esp. lung SCC)
	ADCs (eg, **trastuzumab-deruxtecan**)	ILD/pneumonitis; Rx: d/c → steroids
	IO (eg, anti-PD-1/PD-L1)	Pneumonitis; Rx: d/c → steroids
Nephrotoxicity/ urologic toxicity	Platinum Rx (**cisplatin**)	Esp. proximal tubule; pretreat w/ IV saline
	Methotrexate	Via deposition; Rx: alkalinize urine, IVF
	Cyclophosphamide	Hemorrhagic cystitis; Rx: Mesna
Neurotoxicity (*Sem Oncol* 2006;33:324)	Platinum Rx (**cisplatin**)	"Stocking-glove" neuropathy; ototoxicity
	Cytarabine	Cerebellar toxicity (irreversible 5–10%)
	Methotrexate (esp. intrathecal)	Late leukoenceph, meningitis; reverse w/ intrathecal glucarpidase, leucovorin

	Ifosfamide	Enceph; Rx: methylene blue, thiamine
	Taxanes, vincristine	Sensorimotor long fiber neuropathy
Hepatotoxicity (*Sem Oncol* 2006;33:50)	TKI (eg, imatinib, nilotinib)	↑ LFTs, rarely necrosis; Rx: d/c ± steroids
	Gemcitabine	Common ↑ ALT/AST; ↓ dose if ↑ bili
	Methotrexate	↑ ALT/AST, rarely fibrosis
Dermatologic	TKI (eg, imatinib)	Dermatitis, can be severe (eg, SJS)
	EGFR and MEK inhibitors	Acneiform rash. Rx: steroids + abx.
	Capecitabine, 5-FU, doxil	Hand–foot syndrome
Gastrotoxicity (*Clin Pharm* 2018;57:1229)	Irinotecan	AChE surge, diarrhea w/in 24 hrs
	5-FU	Mucositis, diarrhea
	RAS/EGFR inhibitors	Mucositis, diarrhea
	CDK4/6 inhibitors (esp. abemaciclib)	Diarrhea

*See “ImmunoRx” for cytokine release and immune effector cell–associated neurotoxicity syndromes

PNEUMONIA

Definitions and clinical manifestations

- Pneumonia: s/s (fever, cough, purulent sputum, dyspnea) + new infiltrate on chest imaging
- *Community-acquired* (CAP): acquired outside of hospital setting; *hospital-acquired* (HAP): acquired ≥48 hrs after hosp.; *ventilator-associated* (VAP): acquired ≥48 hrs after intub.
- Lung empyema: accumulation of pus in pleural space
- Lung abscess: parenchymal necrosis with confined cavitation
- Aspiration pneumonitis: acute lung injury after inhalation of gastric contents without infection, though bacterial infection can occur within 24–72 hrs of injury

Microbiology of Pneumonia	
Clinical Setting	**Etiologies**
CAP (*AJRCC* 2019;200:7)	*No pathogen identified in 50–60%*, virus alone in ~25%, bacteria alone in ~10%, virus–bacteria coinfection in <5% Viruses: influenza, RSV, hMPV, parainfluenza, rhinovirus, coronavirus *S. pneumoniae* (most common bacterial cause) *S. aureus* (espec. post-influenza) *Mycoplasma*, *Chlamydia* (espec. in young & healthy) *H. influenzae, M. catarrhalis* (espec. in COPD) *Legionella* (espec. in elderly, smokers, ↓ immunity, TNF inhibitors) *Klebsiella* & other GNR (espec. in alcohol use disorder & aspiration)
HAP/VAP	*S. aureus, Pseudomonas, Klebsiella, E. coli, Enterobacter, Acinetobacter, Steno*. IV abx w/in 90 d risk factor for MDR. Viral ~20% cases.
Empyema	*S. pneumo, S. aureus, E. coli*, *Klebsiella*, *H. influenzae*, anaerobes
Lung abscess	Often polymicrobial, incl. oral flora. *S. aureus,* anaerobes*, Strep* (*anginosus,* GAS), GNR (*Klebsiella, E. coli, Pseudomonas*)*, Nocardia, Actinomyces,* fungi, mycobacteria, *Echinococcus.*
Immunosupp.	Above + *Pneumocystis*, *Cryptococcus*, *Nocardia*, non-TB mycobacteria (NTM), CMV, invasive molds

Diagnostic studies (*AJRCC* 2019;200:e45)

- **Sputum Gram stain/cx:** reliable if high quality (ie, sputum not saliva; <10 squam cells/lpf). If bacterial PNA should be purulent (>25 PMN/lpf). Yield ↓ >10 h after abx (*CID* 2014;58:1782).
- **Procalcitonin:** ↑ in acute bacterial (not viral) PNA. Consider stopping abx if levels <0.25 (<0.5 in ICU) or ↓ ≥80% from peak. ↓ abx by 2–3 d. Not validated if immunosupp. Levels harder to interpret in CKD. False ⊕ in cardiac arrest, shock, burns, surgery.
- **CXR** (PA & lateral; see Radiology inserts)
- HIV test (if unknown); MRSA nares swab in HAP/VAP (if ⊖ 96% NPV for MRSA PNA)
- Consider in severe disease (otherwise not recommended):
  - *Legionella* urinary Ag (detects *L. pneumophila* L1 serotype, 60–70% of clinical disease)
  - *S. pneumoniae* urinary Ag (Se 70%, Sp >90%)
  - Blood cultures (*before antibiotics!*): ⊕ in ~10% of inPts, depending on pathogen
- If clinical suspicion for mTB: (induced) sputum AFB stain ×3 q≥8h (w/ ≥1 early morning).

Mycobact. cx (*empiric respiratory isolation while pending*); mTB DNA PCR if smear ⊕.
- **Viral testing** (DFA or PCR) on nasopharyngeal swab or sputum
- Bronchoscopy: immunosupp., critically ill, failure to respond, suspected PCP, inadequate/ ⊖ sputum cx (send Gram stain/cx, *Legionella* cx, fungal cx/wet prep, mycobacterial cx/smear, modified AFB stain, galactomannan)
- Reasons for failure to improve on initial treatment:
  Insufficient time: may take ≥72 h to see improvement (fever persists >4 d in ~20%)
  Insufficient drug levels for lung penetration (eg, vanco trough <15–20 µg/mL)
  Resistant organisms or superinfxn: eg, MRSA, *Pseudo.;* consider **bronchoscopy**
  Wrong dx: fungal/viral, chemical pneumonitis, PE, CHF, ARDS, DAH, ILD; **consider CT**
  Parapneumonic effusion/empyema/abscess: if CXR ⊖, **consider bedside US or CT**. If effusion >1 cm, drain & send fluid pH, gluc, Gram stain, & cx.
  Metastatic infection (eg, endocarditis, septic arthritis)

Triage

- **qSOFA** predicts poor outcomes, prolonged ICU stay, and in-hospital mortality if >2 of 3: RR >22, AMS, SBP <100 (*JAMA* 2016;315:801)

Treatment (*NEJM* 2023;389:632; *AJRCC* 2019;200:e45)	
Scenario	**Regimen**
CAP (outPt)	Amoxicillin, azithro, or doxy (*avoid* latter two if >25% resistance locally)
CAP (ward)	[3rd-gen ceph + azithro] *or* levoflox; + macrolide to ↑ clinical response (*Lancet Resp Med* 2024;12:294)
CAP (ICU)	3rd-gen ceph + azithro. Only cover MRSA or *Pseudomonas* if risk factors (prior PsA PNA, MRSA infection, recent hospitalization, IV abx)
HAP/VAP	[Pip-tazo *or* cefepime *or* carbapen.] + [vanc or linezolid]. May add resp FQ or azithro if concerned for atypicals. Daptomycin not active in lungs.
Empyema/ abscess	[3rd-gen ceph + MNZ] *or* amp-sulbactam. Only cover *Pseudomonas* or MRSA if risk factors. Empyema: drain if >1 cm ± chest tube. Abscess: drainage not required. De-escalate to PO abx based on clinical improvement & micro.

- Avoid quinolones if suspect TB. When possible, de-escalate abx based on sensitivities.
- Steroids: may ↓ mech vent, ARDS, & mortality in severe CAP (CRP >204 mg/L) (*Lancet Resp Med* 2025;13:221), but ↑ hyperglycemia & readmission. *Avoid* in influenza.
- Duration: CAP: 5–7 days, can de-escalate IV abx to PO after clinical improvement. HAP/VAP: 7 days. Empyema/abscess: 2–6 wks based on complexity, drainage.

Prevention

- All persons ≥50 or age 19–49 w/ CHF, lung disease, cirrhosis, DM, EtOH, smoker, immunosupp. (eg, ESRD, organ transplant, HIV, leukemia, lymphoma, asplenia)
- No prior vax: 1 dose of PCV-21, PCV-20, or PCV15/PPSV23 series

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Viral Respiratory Infections

URI, bronchitis, bronchiolitis, pneumonia (*AJRCCM* 2019;200:e45; *Eur J Radiol* 2021;136:109548)

Microbiology & epidemiology (http://www.cdc.gov/fluview)

- Typical pathogens: Short, mild = rhinovirus, other non-SARS-CoV-2 coronavirus.

Longer, more severe or complicated = **influenza**, parainfluenza, RSV, adenovirus, metapneumovirus, COVID-19 (vide infra). Can be esp. severe in immunosupp.

Diagnosis

- Sx: fever, cough, myalgias, SOB, wheezing, sore throat, rhinorrhea, malaise, confusion
- Respiratory viral panel on nasal swab or sputum/BAL; rapid flu *nasopharyngeal swab* preferred to nasal swab (Se 50–70%, Sp >90%); RT-PCR for flu A/B (>95% Se & Sp)

Treatment (*NEJM* 2017;390:697)

- **Influenza (A & B):**
  - Neuraminidase inhib. (eg, oseltamivir); must start w/in 48 h of sx for low risk; for critically ill or immunosupp., start ASAP even if >48 h. Peramivir IV if unable to tolerate PO.
  - Endonuclease inhib. (baloxavir), superior to oseltamivir in ↓ sx & viral load on 1st day of Rx, but resistance emerging; no data in severe influenza (*NEJM* 2018;379:913)
- **RSV:** can consider inhaled ribavirin in immunosupp, but very expensive & rarely used

Prevention

- Inactivated **influenza vaccine**: rec for *all* >6 mo of age; **RSV** vaccine if >75 or ≥60 + ↑ risk
- Isolation, droplet precautions for inpatients strongly recommended
- Ppx for high-risk contacts of confirmed influenza: oseltamivir × 7 d or baloxavir single dose

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Coronavirus (COVID-19)/SARS-CoV-2 Infection

Microbiology & epidemiology

- Person-to-person transmission via respiratory particles; asx & pre-sx transmission can occur
- Incubation period: up to 14 days, median time of 4–5 days from exposure to sx onset

Presentation

- Ranges from asx to severe illness. Of those with sx, 81% mild-to-moderate, 14% severe (hypoxia), 5% critical (ARDS, shock, multiorgan failure) (*JAMA* 2020;323:13).
- Common sx: fever, chills, cough, dyspnea, myalgias, HA, N/V, diarrhea, loss of smell/taste
- Risk factors for severe illness: age ≥65, CVD, DM, stroke, lung dx, CKD, obesity

Diagnosis

- RT-PCR testing of nasopharynx, lower respiratory tract, or anterior nares
- Rapid antigen testing of anterior nares (less Se than PCR)
- CXR: typically bilateral opacities (esp peripheral), can be nl early; consider CT if dx unclear

Treatment (www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/)

- Nonhospitalized: nirmatrelvir/ritonavir (Paxlovid) (check DDI) or remdesivir > molnupiravir
- Hosp. w/ suppl O_2: dexamethasone (6 mg qd × up to 10 d) ± remdesivir
- Hosp. w/ mechanical ventilation or ECMO: dexamethasone + anti-IL6 (tocilizumab/ sarilumab) or anti-JAK (baricitinib/tofacitinib) if rapidly ↑ O_2 requirement but not intubated
- Anticoag. due to high rate of thrombosis; Ppx vs. Rx dosing based on severity and risk

Prevention

- Vaccines against spike protein highly effective. Infxn may occur but severity much lower.

- CDC isolation guidance (www.cdc.gov/respiratory-viruses/prevention/precautions-when-sick.html)

FUNGAL INFECTIONS

Fungal diagnostics

- **Antigen detection**
  - **1,3-β-D glucan** (Se 75%, Sp 85%): **Candida, Aspergillus, Histo, Coccidio, PCP**, *for invasive infxn in immunosupp. host*. *Cannot* detect Mucor, Rhizopus, Blasto, Crypto.
  - **Galactomannan** (Se 71%, Sp 89%): **Aspergillus**. BAL preferred. Test *serum* only if heme malig or HSCT. Not for screening or Rx monitoring in solid organ txp, chronic granulomatous disease (false ⊕ w/ colonization).
  - **Histo urine/serum Ag**: Se of urine Ag 90% (serum 80%) if dissem; Sp limited by X-react
  - **Crypto Ag** (serum, CSF): sAg >90% Se & Sp in invasive, less for pulm. only unless HIV+
  - **Blastomyces:** urine >serum Ag, high Se but modest Sp given X-react w/ other fungi
- **Culture**: *Candida* grows in blood/urine cx, but ↓ Se of BCx in deep tissue infection; others (eg, *Crypto*, *Histo*) ↓↓ Se of BCx; if suspect *Coccidio* alert lab *(biohazard)*
- **Antibody detection**: useful for *Coccidio* (serum IgG and IgM 7–21 days postexposure)
- **Biopsy**: no grinding of tissue if Zygomycetes suspected

Candida species

- **Microbiology:** normal GI flora; *C. albicans* & nonalbicans spp.
- **Epidemiology:** neutropenia, immunosupp., broad-spectrum abx, intravascular catheters (esp. if TPN), IVDU, abd surgery, DM, renal failure, age >65
- **Clinical manifestations:**
  - Mucocutaneous: cutaneous (eg, red, macerated lesions in intertriginous zones); oral thrush (exudative, erythematous, or atrophic; if unexplained, r/o HIV); esophageal (odynophagia; ± oral thrush); vulvovaginal, balanitis
  - **Candiduria:** typically *colonization* due to broad-spectrum abx and/or indwelling catheter
  - **Candidemia:** ⊕ *blood cx are never a contaminant!* R/o retinal involvement (ophtho consult) & endocarditis w/ TTE ± TEE (esp. w/ prosthetic valve) as req ↑ Rx duration. May present w/ erythematous papules or pustules in immunosupp.
  - *Candida* in sputum: usually not a clinically significant pathogen
  - **Hepatosplenic:** typically, after prolonged neutropenia as cell counts are recovering

Treatment (*CID* 2016;62:409)	
Mucocutaneous	Clotrimazole, nystatin, fluconazole, itraconazole
Candiduria (*if pyuria or sx of infxn*)	Fluconazole or intravesical ampho if severe infxn, immunosupp. or planned GU procedure
Candidemia w/o neutropenia	**Echinocandin** (mica 1st line) if stable w/o prior azole expo-sure can consider fluc; *remove CVC*; test for azole-resist.
Candidemia w/ neutropenia	**Echinocandin** *or* ampho; *remove CVC*; test for azole-resist.

Aspergillosis (*Lancet* 2021;397:499)

- **ABPA:** airway hypersensitivity secondary to *Aspergillus* colonization
- **Chronic pulmonary aspergillosis:** includes aspergilloma (fungus ball), pulm. nodules, chronic

cavitary and chronic fibrotic pulmonary aspergillosis that can present with subacute cough, dyspnea, hemoptysis; aspergilloma/nodules can be asymptomatic
- **Invasive aspergillosis:** seen in immunosupp., esp prolonged neutropenia. Primarily pulmonary, ie, PNA w/ *chest pain*, cough, *hemoptysis*; CT: solid/cavitary nodules, halo sign. Non-pulm. : rhinosinusitis (like *Zygomycetes*), CNS (brain abscesses, mycotic aneurysm), endophthalmitis (eye pain, visual changes), cutaneous, GI (typhlitis).
  Rx: voriconazole or posaconazole preferred over ampho. For aspergilloma, ± resection.

Zygomycetes (eg, ***Mucor, Rhizopus***)

- **Epidemiology: diabetes** (espec. those w/ prior DKA), heme malignancy, neutropenia, transplant, chronic steroids, iron overload, trauma, h/o voriconazole Rx or Ppx
- **Clinical: rhinocerebral** = severe periorbital/facial pain, swelling, vision changes, sinusitis, ophthalmoplegia, nasal ulcerations/necrosis, HA. Other: **pulm.** (PNA w/ infarct & necrosis); **cutaneous** (indurated painful cellulitis ± eschar); **GI** (necrotic ulcers); **renal** (flank pain, fever).
- **Treatment** (high mortality): 1st line is debridement + ampho. Can de-escalate to posaconazole or isavuconazole if improving after debridement.

Endemic Fungi

Cryptococcus (*NEJM* 2024;390:1597; *Lancet ID* 2024;24:e495)

- **Epidemiology:** immunosupp. most susceptible (espec. AIDS, transplant recipients, and cirrhosis); can occur in healthy hosts (esp *C. gattii*)
- **Clinical manifestations**
  CNS (meningoencephalitis): subacute HA, fever, meningismus, CN abnl, ± stupor
  Other sites: pulm., GU, cutaneous, CNS cryptococcoma. *With any crypto dx, LP all Pts.*
- **Dx:** CSF cell counts vary in HIV vs. non-HIV; serum/CSF CrAg (Se 99%, Sp 86–100%); cx
- **Treatment**
  CNS Rx: induction (ampho 1–2 wks ± flucytosine 2 wks), consolidation and maintenance (fluconazole) phases (*NEJM* 2013;368:1291); if ↑ ICP, may need repeat LP/VP shunt
  Non-CNS disease (pulm., skin, bone, blood) in HIV ⊖ Pts: consider fluconazole

Histoplasmosis (*CID* 2007;45:807; *NEJM* 2024;390:536)

- **Epidemiology**: endemic to central & SE U.S., but sporadic cases throughout U.S.
- **Clinical manifestations**
  Acute: PNA ± hilar LAN, often subacute, but high inoculum can cause acute severe PNA
  Chronic lung disease: cough + "B" sx ± cavitary lesions (Ddx TB, blasto)
  Disseminated (seen in immunosupp.): fever, fatigue, wt loss, mucocutaneous lesions, ΔMS, arthritis, pericarditis, interstitial infiltrates, HSM, LAN, cytopenias
- **Treatment:** mild to mod: itraconazole; disseminated/severe: ampho → itraconazole

Coccidioidomycosis (*CID* 2016;63:112; *NEJM* 2024;390:536)

- **Epidemiology**: endemic to SW U.S., Central and South America
- **Clinical manifestations**
  Acute: subclinical PNA, arthralgias, rash (erythema nodosum)
  Chronic lung disease (seen in immunosupp): dyspnea, chest pain, hemoptysis, "B" sx
  Disseminated (immunosupp, pregnant): meningitis, osteo, monoarthritis, cutaneous
- **Treatment:** consider azoles for mild PNA in immunosupp.; ampho for severe/CNS involvement; azoles for extrathoracic w/o CNS involvement; some cases require debridement

Blastomycosis (*CID* 2008;46:1801)

- **Epidemiology** endemic to the eastern ½ of U.S.
- **Clinical manifestations**
  Acute: PNA w/o hilar LAN that can progress to ARDS
  Chronic: cough + "B" sx, fibronodular infiltrates, masses ± cavitary lesions (Ddx TB, histo)
  Disseminated (seen in immunosupp.): rash (verrucous, ulcerated lesions), subcutaneous nodules, osteo, GU (prostatitis, epididymo-orchitis), CNS involvement uncommon
- **Treatment:** mild to mod: itraconazole; disseminated/severe/CNS: ampho → itraconazole

INFXNS IN IMMUNOSUPPRESSED HOSTS

Overview

- Many Pts have ≥1 risk (eg, DM, ESRD, transplant, extremes of age)
- Accurate dx of opportunistic infections and targeted Rx key in this population
- The following is not an exhaustive list, but a delineation of common or classic etiologies

Predisposition	Classic Infectious Etiologies
Humoral immune dysfunction (eg, CVID, myeloma) and **asplenia**	**Encapsulated bacteria:** *S. pneumo*, *H. flu*, *N. meningitidis* (vaccinate against these 3, ideally prior to splenectomy) **Other bacteria:** *E. coli* and other GNRs, *Capnocytophaga* **Parasites:** *Babesia, Giardia;* **Viruses:** VZV, echovirus, enterovirus
Granulocytopenia or neutropenia (includes DM, ESRD → functional impairment)	**Bacteria:** Gram positive: coag ⊖ staph, *S. aureus*, viridans strep, *S. pneumo*, other strep; *Corynebacterium* spp., *Bacillus* spp. Gram negative: *E. coli*, *Klebsiella*, *Pseudomonas* **Fungi:** Yeast: *Candida albicans* and other *Candida* spp. Molds: *Aspergillus, Mucor* spp., endemic fungi, and others **Viruses:** VZV, HSV-1 and -2, CMV
Impaired cell-mediated immunity (CMI) (eg, HIV/AIDS, chronic steroids, posttxp, DM, ESRD, autoimmune dis.)	**Bacteria:** *Salmonella spp., Campylobacter, Listeria, Yersinia, Legionella* (*Lancet* 2016;387:376)*, Rhodococcus, Nocardia,* TB, non-TB mycobacteria **Fungi:** *Candida, Crypto, Histo, Coccidio, Aspergillus, Pneumocystis, Zygomycetes* spp. and other molds **Viruses:** HSV, VZV, CMV, EBV, JC virus, BK virus **Parasites:** *Toxo., Crypto., Isospora, Microsporidia, Babesia, Strongy.*
Organ dysfunction	**Liver (esp. cirrhosis):** *Vibrio* spp., encapsulated bacteria **ESRD:** impaired granulocyte fxn and CMI as above Iron overload (or deferoxamine Rx): *Yersinia*, *Zygomycetes*
Biologics (eg, TNF inhibitors, anti-B-cell Rx; ✓ for TB before starting)	**Bacteria:** sepsis, septic arthritis, TB, NTM, *Listeria*, *Legionella* **Fungi:** *Pneumocystis, Histo, Coccidio, Aspergillus*, endemic fungi **Viruses:** JC virus (PML), EBV, HSV, VZV, HBV **Parasites:** *Strongyloides* reactivation

(*ID Clin North Am* 2019;33:361; *Microbiol Spectr* 2016;4:DMIH2-0026-2016; *Clin Transplant* 2019;33:e13499)

URINARY TRACT INFECTIONS

Definitions

- **Asymptomatic bacteriuria:** presence of bacteria in urine without signs or sx of infection
- **Uncomplicated:** confined to bladder. No upper tract or systemic infection signs.
- **Complicated:** extends beyond bladder (pyelonephritis, renal/perinephric abscess, prostatitis) with symptoms of fever, rigors, malaise, flank pain, CVA tenderness, or pelvic/perineal pain. More likely to develop bacteremia or sepsis. Men, those w/ nephrolithiasis, strictures, stents, urinary diversions, immunosupp, DM, are not automatically complicated. Pregnant & renal txp *are* considered complicated.

Microbiology

- Uncomplicated: ***E. coli*** (80%), *Proteus*, *Klebsiella*, *S. saprophyticus* (*CID* 2004;39:75). In healthy, nonpregnant women, lactobacilli, enterococci, Group B strep, and coag-neg staph (except *S. saprophyticus*) are likely *contaminants* (*Annals* 2012;156:ITC3).
- Complicated: as above + PsA, enterococci, staph (uncommon 1° urinary pathogen w/o catheter or recent instrumentation; ? bacteremia w/ hematogenous spread). ↑ MDR.
- Catheter-associated: *E. coli* most prevalent, *Candida*, *Enterococcus,* PsA, other GNR
- Urethritis: *Chlamydia trachomatis, Neisseria gonorrhoeae, Ureaplasma urealyticum, Trichomonas vaginalis, Mycoplasma genitalium*, HSV

Clinical manifestations

- **Cystitis: dysuria**, **urgency**, **frequency**, hematuria, suprapubic pain; fever *absent.* R/o vaginitis if symptoms of cystitis & urethritis. Neurogenic bladder Pts may have atypical sx (↑ spasticity, autonomic dysreflexia, malaise).
- **Urethritis:** dysuria, urethral discharge (see "STI")
- **Prostatitis**
  Chronic: similar to cystitis + *symptoms of obstruction* (hesitancy, weak stream)
  Acute: perineal pain, fever, tenderness on prostate exam
- **Pyelonephritis:** fever, chills, flank or back pain, nausea, vomiting, diarrhea
- **Renal abscess**: pyelonephritis sx + *persistent fever on appropriate antibiotics*

Diagnostic studies (*NEJM* 2016;374:562)

- **Urinalysis: pyuria** + bacteriuria ± hematuria ± nitrites
- **Urine cx** (clean-catch midstream or straight-cath)
  Obtain cx only if symptoms (although in ill Pts, can include ΔMS, autonomic instability)
  ⊕ if: ≥10^5 CFU/mL, though <10^5 but ≥10^2/mL may still indicate UTI in some scenarios
  Pyuria & ⊖ UCx=sterile pyuria. Ddx: prior abx, nephrolithiasis, interstitial nephritis, tumor, TB, urethritis (see "STI").
- **Catheter-associated:** requires (1) s/s (incl atypical) + (2) urine cx w/ 1 species ≥10^3 colonies from clean urine sample (**after** replacing Foley). Pyuria alone *not* sufficient to dx.
- Blood cultures: obtain in febrile Pts; consider in complicated UTIs
- For all men w/ UTI, consider prostatitis: ✓ prostate exam
- CT A/P: consider in severely ill, obstruction, persistent sx after 48–72 hours of approp abx

Treatment of UTIs (*CID* 2011;52:e103; *JAMA Netw Open* 2024;7:e2444495)	
Scenario	**Empiric Treatment Guidelines** (narrow based on UCx)
Asymptomatic bacteriuria	Do *not* treat. Exceptions: pregnant women, recent (1-2 mo) renal txp, prophylaxis prior to invasive urologic procedures (*CID* 2019;68:1611).
Cystitis (*JAMA* 2014;16:1677)	Uncomp: nitrofurantoin (Macrobid 100 mg PO q12h or Macrodantin 100 mg PO q6h) × 5 d *or* TMP–SMX DS × 3 d *or* fosfomycin (3 g × 1). Refer to dosing guidelines for ↑ Cr. Sulopenem etzadroxil & probenecid and pivmecillinam FDA approved in 2024 as PO options for uncomplicated UTI with limited alternative therapies.

	Complicated: outPt FQ or TMP–SMX PO × 7–14 d FQ or TMP–SMX superior to β-lactams (*NEJM* 2012;366:1028) InPt: CTX or FQ; PO if improving, if growing GPC add vancomycin If catheterized **remove or exchange catheter**
Prostatitis	FQ or TMP–SMX PO × 14–28 d (acute) or 6–12 wk (chronic)
Pyelonephritis	OutPt: FQ × 7 d *or* TMP–SMX PO × 14 d (*Lancet* 2012;380:452) InPt: CTX × 14 d; if at risk for MDR pathogen cefepime, pip-tazo, carbapenem, or plazomicin (*NEJM* 2019;380:729) (Δ IV → PO when clinically improved & afebrile 24–48 h, tailor to cx)
Renal abscess	Drainage + antibiotics as for pyelonephritis

SEXUALLY TRANSMITTED INFECTIONS

Risk factors and screening (*MMWR* 2021;70:1)

- **High risk:** >10 lifetime sexual partners, prior STI, MSM, sex workers
- Screening recommendations: differ based on sexual practices and risk. All adults should have one-time HIV Ag/Ab, HCV Ab. Consider q3mo testing for STIs if high risk.

Genital Lesions (*MMWR* 2021;70:1)		
	Disease	**Symptoms**
Painless	Syphilis (*T. pallidum*)	1°: **chancre** = firm, indurated, clean base 2°: fever, LAN, rash palms/soles, uveitis, condylomata lata 3°: aortitis, gumma, CN palsies (7/8), tabes dorsalis, meningitis Latent = asx; early latent <1 yr; late >1 yr/unknown
	LGV (*C. trachomatis, L1–L3*)	1°: transient papule 2°: 2–6 wks later, painful inguinal LN (buboes) 3°: Anorectal syndrome w/ proctitis, ulcers
	Donovanosis/GI (*K. granulomatis*)	Multiple beefy, firm, irregular ulcers (“granuloma inguinale”), no LAN; in tropics
Painful	Genital herpes (HSV2>1)	Prodrome: multiple painful vesicles 1° outbreak: more severe ± LAN/fever
	Mpox	± Prodrome, ± LAN. Pharyngitis, proctitis, and/or enteritis possible. Macular → popular → vesicular → pustular ± umbilication.
	Chancroid (*H. ducreyi*)	Multiple ulcers ± LAN, in tropics

Diagnosis (*MMWR* 2021;70:1; *JAMA* 2022;327:161; *HIV Med* 2024;25:910)

- Syphilis: 1st step is treponemal test: IgG to *T. pallidum*. ⊕ for life.
  2nd step: confirm w/ non-treponemal test (VDRL/RPR titer). Should ↓ 4-fold w/ Rx.
  Neurosyphilis: LP not needed if only ocular or otic sx. CSF VDRL may be ⊖.
- LGV: clinical dx + ⊕ rectal *C. trachomatis* NAAT + r/o other causes of proctitis

- Donovanosis: bx w/ Donovan bodies (encapsulated GNR) in monocytes/macrophages
- Genital herpes: clinical dx; confirm w/ PCR, viral cx from lesion
- Chancroid: clinical dx; r/o syphilis & HSV
- Mpox (+PPE): vigorous swab of skin lesion for PCR; no unroofing (injury risk). r/o STIs.

Treatment (*MMWR* 2021;70:1; *JAMA* 2022;327:161; *HIV Med* 2024;25:910)

- Syphilis: 1°/2°/early latent: PCN G benzathine 2.4 mil U IM × 1; 3°/late latent: PCN G 2.4 mil U IM × 3; Neuro: IV PCN G 4 mil U q4h 10–14 d (*CID* 2011;53:S110)
- LGV: doxy 100 mg BID × 21 d + aspiration of buboes
- Donovanosis: azithro 1 g qwk × 3 wks, until healed (*MMWR* 2015;64:1)
- Genital herpes: valacyclovir 1 g bid × 7–10 d. Consider suppression if >6 outbreaks/yr.
- Chancroid: azithro 1 g × 1 PO *or* cipro 500 mg bid × 3 d
- Mpox: tecovirimat in immunosuppressed Pts (eg, uncontrolled HIV, espec. CD4 <350). Investigational, efficacy uncertain. ID consult.

Genital Discharge (*MMWR* 2021;70:1)	
Disease	**Symptoms**
Gonorrhea (*N. gonorrhoeae*) & Chlamydia (*C. trachomatis*)	Va: Mucopurulent cervicitis, dysuria, PID; can be asx Pe: Urethritis, infxn of epididymis/prostate All: pharyngitis
Mycoplasma genitalium	Suspect in Pts w/ urethritis/cervicitis after Rx for GC/CT
Trichomoniasis (*T. vaginalis*)	Va: Malodorous purulent discharge, dysuria, dyspareunia Pe: Asymptomatic
Bacterial vaginosis (*Gardnerella vaginalis*)	Va: Malodorous gray/white discharge, no dyspareunia

Va denotes all persons with a vagina. Pe denotes all persons with a penis.

Diagnosis (*MMWR* 2021;70:1; *JAMA* 2022;327:161)

- NAAT (Va: vaginal/cervical/urine; Pe: urine), mycoplasma testing not widely available
- For GC/CT, strongly suggest urine + rectal/pharyngeal swab if history of oral or anal sex
- Trichomoniasis: motile trichomonads on wet mount
- Bacterial vaginosis: clue cells on wet mount; ⊕ whiff test; vaginal culture

Treatment (*MMWR* 2021;70:1; *JAMA* 2022;327:161)

- GC: CTX 500 mg IM × 1 (if wt >150 kg, 1 g). CT: doxy 100 mg PO bid × 7 d (preferred) or azithro 1 g PO × 1. Do *not* need to treat both if neg NAAT. Retest at 3 mos.
- *M. gen.*: doxy 100 mg PO bid × 7 d, then: moxifloxacin 400 mg PO qd × 7 d
- Trich: Va → MNZ 500 mg PO bid *or* tinidazole 2 g PO qd × 7 d. Pe → MNZ 2 g PO × 1.
- Bacterial vaginosis: MNZ 500 mg PO bid × 7 d *or* vaginal Rx w/ MNZ gel daily × 5 d

SKIN AND SOFT TISSUE INFECTIONS

Definitions

- **Cellulitis:** infection of dermis and subcutaneous tissue characterized by erythema, warmth, tenderness, and swelling; often occurs as a result of skin breaches (*JAMA* 2016;315:3)

- **Skin abscess:** subcutaneous collection of pus
- Staph toxic shock syndrome: rapid onset fever, sunburn rash, hypotension, and multiorgan injury. *Staph aureus* cx are not necessary for dx. Often associated with packing (tampon, nasal packing). Management may require surgical debridement + abx.

Risk factors

- Trauma, edema, preceding skin inflammation or infection, obesity, DM, other immunosupp.

Microbiology (*CID* 2014;59:e10)

- Purulent: **MRSA** (*NEJM* 2006;355:666) causes up to 75% of purulent skin/soft-tissue infections, followed by MSSA and strep
- Non-purulent: *Strep*, MSSA, aerobic GNRs. MRSA less commonly unless significant risk factors (prior MRSA infection, IVDU, HD, recent abx, or hospitalization).
- Bites: **skin** (***Strep*, *Staph*** [MRSA only if risk factors]) and **oral flora** (including anaerobes) + special exposures:

Feature	Microbiology	Clinical	Treatment
Cat bite*	*Pasteurella spp.*	Rapid onset erythema, swelling, lymphangitis, fever	Amox/clav
Dog bite	*Pasteurella & Capnocytophaga spp.*	Can cause severe sepsis w/ DIC & gangrene in asplenia/cirrhosis and other immunosupp.	Amox/clav If Capno. suspected: pip/tazo or carbapenem
Penetrating injury	*Pseudomonas*	Can be a/w deep tissue abscess	Directed based on suscept.
Gardening	*Sporothrix*	Ulcerating nodules, lymphatic spread	Itraconazole
Salt H_2O or raw oysters/fish	*V. vulnificus* (Northern limit Cape Cod, MA)	Hemorrhagic bullae & sepsis (esp. cirrhosis, Fe overload state)	Doxy + Ceftaz/CTX
	Mycobacterium marinum	Indolent, nodules on extremities/ superficial lymphadenitis	Macrolide + rifampin/ ethambutol
Fresh H_2O	*Aeromonas*	Myonecrosis/rhabdo can occur	FQ, TMP-SMX, or CTX

*Cat scratch disease caused by *Bartonella* acquired via cat scratch or bite. Results in lymphadenitis.

Diagnosis

- Clinical diagnosis based on physical examination
- Cultures from intact skin are not helpful and should *not* be performed (*CID* 2014;59:e10)
- BCx are typically low yield (~5–10%)
- Ultrasound can be used to identify deep abscesses and facilitate drainage. If abscess is found, incision/drainage is key to treatment.
- Aspirate from an abscess may provide microbiologic dx

Cellulitis Treatment (*CID* 2014;59:e10; *ID Clin North Am* 2021;35:49)			
Purulent	**Usual Micro**	**Severity**	**Treatment**
No	β-hemolytic *Strep* >*S. aureus*	Mild	Oral: PCN VK, 1st-gen cephalosporin
		Mod	IV: PCN, ceftriaxone, cefazolin

		Severe	IV: vanc + pip/tazo (± clinda or linezolid for toxic shock syndrome)
Yes	*S. aureus* (incl. MRSA) >> β-hemolytic *Strep*	Mild	I&D + clinda or TMP–SMX (*NEJM* 2017;376:2545)
		Mod	I&D + TMP–SMX or doxycycline or linezolid
		Severe	I&D + IV vanc, daptomycin, or linezolid (± clinda or linezolid for toxic shock syndrome)

Mild: abscess <2 cm, no systemic signs of infection, immunocompetent, no indwelling hardware; moderate: systemic signs; severe: SIRS or immunosuppressed

- **Limb elevation;** erythema may *worsen* after starting abx b/c bacterial killing → inflam.
- In obese Pts, adequate drug dosing important to avoid treatment failure (*J Infect* 2012;2:128)
- **Duration:** 5 to up to 14 d based on severity and response to treatment. Take pictures & draw margins to track progress. Compression stockings ± PCN ppx if recurrent cellulitis.

Necrotizing Soft-Tissue Infections (*NEJM* 2017;377:2253)

Definition

- Fulminant tissue destruction, systemic toxicity, & high mortality. **Surgical emergency**.
- May include cellulitis, fasciitis, myositis, myonecrosis (gas gangrene)

Risk factors

- Can affect healthy individuals via skin/mucosal breach or traumatic wound, but ↑ risk w/ DM, PVD, EtOH use disorder, IVDU, cirrhosis, or other immunosupp.

Microbiology

- **Necrotizing fasciitis**
- Type I: polymicrobial (mixed aerobes & anaerobes), typically in older Pts w/ above RFs. **Fournier's gangrene** involves genitalia and/or perineum.
  Head and neck NSTI evolve from oral flora including anaerobes.
- Type II: monomicrobial, usually group A strep, less likely *Staph, Vibrio, Aero.*; a/w TSS
- **Clostridial myonecrosis (gas gangrene):** *C. perfringens; C. septicum* (large Gram ⊕ rods w/ blunt ends on Gram stain). A/w traumatic wounds that create an anaerobic environment ideal for *Clostridia*.

Clinical manifestations

- Erythema, edema, warmth + **systemic illness** ± **crepitus,** bullae, necrosis
- **Rapid progression** of clinical signs
- **Pain out of proportion** to apparent cellulitis; skin hyperesthetic and later anesthetic

Diagnosis

- Clinical dx is sufficient to initiate **urgent surgical exploration**
- Aspiration of necrotic center; BCx; Gram stain; lactate, AST, & CK for deep tissue necrosis
- Imaging: **non-contrast CT**, but do not delay Rx/surgery (*Arch Surg* 2010;145:452)
- Microbiologic dx from Gram stain and culture of surgical specimens

Treatment (*CID* 2014;60:169)

- Urgent surgical exploration with debridement of necrotic tissue and ID consultation
- Empiric antibiotics: [pip/tazo *or* ceftriaxone + metronidazole *or* carbapenem] + [vanco or

linezolid]. For Group A Strep: penicillin + clindamycin or linezolid (*Lancet ID* 2024;10:S1473; *OFID* 2023;10:ofad258) + consideration of IVIG for toxic shock.

Diabetic Foot Infections (*JAMA* 2023;330:62)

Microbiology and severity (*CID* 2023;ciad527)

- **Mild**: superficial ulcer, no involvement of deeper structures, surrounding erythema >0.5 but <2 cm, and no systemic illness. Usually *S. aureus* or aerobic streptococci.
- **Moderate**: ulcer with involvement of deeper structures, surrounding erythema ≥2 cm, and no systemic illness. More likely to be chronic and polymicrobial (PsA, enterococci, enteric GNR, anaerobes).
- **Severe:** any foot infection + ≥2 SIRS criteria. Anaerobic streptococci, enteric GNR, PsA, *Bacteroides*, *Clostridium.*

Initial evaluation

- Cleanse, debride, probe, and obtain deep anaerobic + aerobic cultures
- Assess for PVD: sensation, pulses, ABIs

Diagnosis

- **Deep tissue wound cx** at time of debridement (ideally prior to antibiotics). Superficial swabs are typically of limited utility due to colonization.
- For mod/severe: obtain blood cx, ESR, CRP
- **Osteomyelitis should always be ruled out.** At ↑ risk if: grossly visible bone or able to probe to bone, ulcer >2 cm, ulcer duration >1–2 wk, ESR >70. If suspicious for osteo, obtain plain films, ESR, CRP, ± MRI (see “Osteomyelitis”).

Treatment (*CID* 2023;ciad527)

- **Mild infxn:** oral abx. Target GPCs (diclox, cephalexin/cefadroxil, or amox/clav); use TMP–SMX or doxy for MRSA.
- **Mod/severe infxn:** IV abx. Target GPCs (vanco, linezolid, dapto) + GNRs (CTX, levo, or amp/sulb) ± anaerobes (metronidazole or clinda). Add PsA coverage (cefepime or pip-tazo) if: macerated wound, significant water exposure, warm climate.
- Elevation, non–weight-bearing status, wound care, glycemic control, Rx for venous insufficiency and arterial ischemia
- **Many require surgery:** early, aggressive, and repeated debridement; revascularization or amputation may be necessary

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Osteomyelitis

Infection of bone due to hematogenous seeding or direct spread from contiguous focus

Etiology (*Lancet* 2004;364:369)

- **Hematogenous: *S. aureus***; mycobacterial infection of vertebral body = Pott’s disease
- **Contiguous focus** (may be acute or chronic)
  Open fracture, orthopedic surgery, etc.: ***S. aureus*** and ***S. epi***
  Skin breakdown + vasc. insuffic. (eg, diabetic foot, pressure ulcer): **polymicrobial**
  GU source (GNR, *Enterococcus*)

Clinical manifestations

- Surrounding soft-tissue compromise ± fistula to superficial skin

- ± Fever, malaise, and night sweats (more common in hematogenous than contiguous)
- Vertebral osteomyelitis (esp. IVDU): unremitting, focal back pain, ± fever (*NEJM* 2010;362:1022)

Diagnosis (*JAMA* 2008;299:806)

- Crucial to obtain cx data of causative organism to avoid long-term empiric abx
- **Bone biopsy** or **tissue cx** obtained surgically or via percutaneous biopsy (send aerobic, anaerobic, mycobacterial, and fungal cultures + pathology) unless ⊕ blood cx. Do not rely on swabs of ulcers or fistulae drainage.
- Physical exam: high suspicion in diabetic foot (vide supra) if can probe ulcer to bone or ulcer >2 cm^2 (Sp 83%, 90% PPV)
- **Blood cultures before antibiotics** (more often ⊕ w/ acute hematogenous osteomyelitis)
- CBC, CRP, ESR (>70 greatly ↑ likelihood of osteo)
- Imaging
  - Plain radiographs: normal early in disease; lytic lesions seen after 2–6 wk
  - **MRI:** preferred imaging study (overall Se 90%, Sp 82%; *Archives* 2007;167:125)
  - CT: can demonstrate periosteal reaction and cortical and medullary destruction
  - CT & MRI very Se but ↓ Sp; false ⊕ if contig focus w/ periosteal reaction, Charcot Δs
  - Radionuclide imaging: very Se but non-Sp (false ⊕ if soft-tissue inflammation)

Treatment

- **Antibiotics:** based on cx data. If clinically stable, consider holding abx until bone bx. Duration depends on Rx strategy/goals of management (eg, 6 wks for vertebral osteo; *Lancet* 2015;385:875). After ≥7 days from either start of IV abx or surgery, if doing well consider (in consultation with ID!) Δ'ing IV to PO (if good bioavailability) (*NEJM* 2019;380:425).
- For osteo related to sacral decubitus ulcer: no role for prolonged abx w/o concomitant surgical intervention and plan for coverage (eg, flap) (*CID* 2019;68:338). Rx for superimposed cellulitis if clinical suspicion.
- **Surgery** should be considered for any of the following: acute osteo that fails to respond to medical Rx, chronic osteo, complications of pyogenic vertebral osteo (eg, neurologic compromise, spinal instability, epidural abscess), or infected prosthesis

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Epidural Abscess

Etiology

- Hematogenous spread (⅔): skin infection, soft tissue (dental abscess), or endocarditis
- Direct extension (⅓): vertebral osteo, sacral ulcer, spinal anesthesia or surgery, LP
- Risk factors: IVDU, diabetes, renal failure, alcohol use disorder, immunosuppression
- ***S. aureus*** most common pathogen; in immunosuppressed, consider fungal, TB, and *Nocardia*

Clinical manifestations

- **Back pain** with spinal or paraspinal tenderness + **fever** ± followed by radiculopathy. *Sx of cord compression or cauda equina is a surgical emergency.*

Diagnostic studies

- **MRI** with contrast
- Aspiration of abscess fluid for Gram stain & cx or operative Gram stain & cx
- Blood cx (frequently ⊖)

Treatment

- **Antibiotics** (typically MRSA and gram-negative coverage initially then narrowed based on

culture data) ± **surgery** (decompressive laminectomy and debridement) for failure to improve on medical Rx. Emergent surgery for early s/s of cord compression (w/ vertebral osteo and epidural abscess).

INFECTIONS OF THE NERVOUS SYSTEM

Acute Bacterial Meningitis

Definition

- Inflammation of tissue around the brain/spinal cord
- Usually arising from nasopharynx (hematogenous spread), bacteremia, or direct inoculation (surgery, contiguous infection, trauma, foreign body [eg, CSF shunt])

Microbiology in Bacterial Meningitis (*NEJM* 2011;364:2016)	
S. pneumoniae (30–60%)	Look for preceding infection (bacteremia, pneumonia, endocarditis) Drug-resistant *S. pneumoniae:* ~40% PCN-resistant (even *intermediate* resistance problematic) ~<10% 3rd-gen. cephalosporin-resistant See "Pneumonia" for *S. pneumoniae* vaccination recs
N. meningitidis (10–35%)	Primarily in age <30 y; associated petechiae or purpura ↑ risk in asplenia, complement defic., HIV, SCT, unvaccinated, eculizumab or ravulizumab Vaccine for all age 11–18 y, HIV infxn, asplenia, C5–9 deficiency
H. influenzae (<5%)	↑ risk in asplenia, complement defic., HIV, SCT, unvaccinated, CSF leak, trauma/surgery, mastoiditis Vaccine for all children; markedly ↓ incidence
L. monocytogenes (5–10%)	↑ in immunosupp (glucocorticoids, transplant), elderly, malignancy, pregnant, cirrhosis. Outbreaks a/w contaminated dairy & raw veg.
GNRs (1–10%)	More common in health care–associated meningitis (*E. coli, Klebsiella sp., Pseudomonas aeruginosa)*
Staphylococci (5%)	Preceding infection (endocarditis, bacteremia), post-CNS surgery, foreign bodies (CSF shunt, intrathecal pump)
Mixed infection	Suspect parameningeal focus or CSF leak, post-CNS surgery

Clinical manifestations (*Lancet ID* 2016;16:339)

- Headache (83%), fever (74%), stiff neck (74%), photosensitivity, GCS <14 (71%), nausea (62%), seizure; **95% have 2 of 4: HA, fever, stiff neck, △MS**
- Presentation may be *atypical* (eg, lethargy w/o fever) in elderly and immunosupp.

Physical exam (*CID* 2002;35:46; *Am J Emerg Med* 2013;31:1601)

- Nuchal rigidity (Se 30%, Sp 68%), Kernig's sign (Se 5%, Sp 95%), Brudzinski's sign (Se 5%, Sp 95%), jolt sign (HA worsens w/ horizontal rotation) (Se 64%, Sp 43%)
- ± Focal neuro findings (~30%; hemiparesis, aphasia, visual field cuts, CN palsies)

- ± HEENT findings: sinus tenderness, clear rhinorrhea (CSF leak)
- ± Skin and joint findings: petechial rash (*N. meningitidis*), genital or oral ulcers (HSV), arthritis with joint effusion (*N. meningitidis*)

Sequential management of bacterial meningitis

1. **Blood cx**, initiate **empiric antibiotics**, consider corticosteroids (vide infra)
2. **CT head** if indicated (vide infra)
3. **LP** ASAP (if not contraindicated); yield of CSF cx unlikely to be changed if obtained w/in ~4 h of initiat of abx

Diagnostic studies (*NEJM* 2017;388:3036)

- **Blood cultures** ×2 *before abx*
- WBC count: >10,000 in >90% of bacterial meningitis in healthy hosts
- Head CT to r/o mass effect before LP *if ≥1 high-risk feature:* immunosupp., h/o CNS disease, new-onset seizure, focal neuro findings, papilledema, GCS <15 (*CID* 2004;39:1267)
- **Lumbar puncture** with opening pressure (*NEJM* 2006;355:e12)
  - Send CSF for cell count and differential, glucose, protein, Gram stain, bacterial cx
  - Additional CSF studies based on clinical suspicion: AFB smear/cx (or MTb PCR), cryptococcal Ag, fungal cx, VDRL, Multiplex PCR (HSV, VZV, enterovirus), cytology
  - CSF Gram stain has 30–90% Se; cx 80–90% Se if LP done prior to abx though abx should not be delayed for LP if there is concern for bacterial meningitis
  - *Rule of 2s:* CSF WBC >2k, gluc <20, TP >200 has >98% Sp for bacterial meningitis
  - Repeat LP only if no clinical response after 48 h of appropriate abx or CSF shunt
  - Metagenomic next-generation sequencing ↑ dx yield (*NEJM* 2019;380:2327)

Typical CSF Findings in Meningitis

Type	Appearance	Pressure (cm H_2O)	WBC/mm^3 Predom Type	Glc (mg/dL)	TP (mg/dL)
Normal	Clear	9–18	0–5 *lymphs*	50–75	15–40
Bacterial	Cloudy	18–30	100–10,000 *polys*	<45	100–1000
TB	Cloudy	18–30	<500 *lymphs*	<45	100–200
Fungal	Cloudy	18–30	<300 *lymphs*	<45	40–300
Aseptic	Clear	9–18	<300 *polys → lymphs*	50–100	50–100

Empiric Treatment of Bacterial Meningitis (*Lancet* 2012;380:1693)	
Adults <50 y	Ceftriaxone + vancomycin (trough 15–20), consider acyclovir IV
Adults >50 y	Ceftriaxone + vancomycin + ampicillin, consider acyclovir IV
Immunosuppressed	[Cefepime *or* meropenem] + vanc ± amp (not nec. if on meropenem), consider acyclovir IV & fungal coverage
Healthcare-assoc. infection (eg,	[Cefepime *or* meropenem *or* ceftazidime] + vancomycin

surgery, CSF shunt)	
When possible, organism-directed Rx, guided by sensi's or local patterns of drug resistance	
Confirm appropriate dosing as *higher doses are often needed in meningitis* (adjust for renal fxn)	
Corticosteroids: If causative organism is unknown, dexamethasone 10 mg IV q6h × 4 d recommended prior to or with initiation of abx. Greatest benefit in *S. pneumoniae* and GCS 8–11 (↓ neuro disability & mortality by ~50%). Avoid in crypto (*NEJM* 2016;374:542).	
Prophylaxis: for close contacts of Pt w/ *N. meningitidis*; rifampin (600 mg PO bid × 2 d) or ciprofloxacin (500 mg PO × 1) or ceftriaxone (250 mg IM × 1). See "Microbiology in Bacterial Meningitis" table for available vaccinations.	
Precautions: droplet precautions until *N. meningitidis* is ruled out	

Aseptic Meningitis

Definition

- Clinical/lab evidence of meningeal inflammation with negative bacterial cx (CSF & blood)

Etiologies (*Neurology* 2006;66:75)

- **Viral**: enteroviruses are most common cause (summer/fall; rash, GI, URI sx), HIV, HSV, VZV, mumps (parotitis), lymphocytic choriomeningitis virus (rodent exposure), encephalitis viruses, adenovirus, polio, CMV, EBV, WNV
- **Focal bacterial infection**: brain/epidural/subdural abscess, CNS septic thrombophlebitis
- **Partially treated bacterial meningitis**
- **Other infectious**: TB, fungal (*Cryptococcus*, *Coccidioides*), Lyme, syphilis, leptospirosis
- **Neoplasm**: intracranial tumors (or cysts), lymphomatous or carcinomatous meningitis
- **Drug-induced** meningitis: NSAIDs, IVIG, antibiotics (TMP–SMX, PCN), anti-epileptics
- **Systemic autoimmune illness**: SLE, sarcoidosis, Behçet's, Sjögren's syndrome, RA
- Mollaret's: recurrent lymphocytic meningitis, spontaneously resolving (often HSV-2)

Diagnosis

- Obtain LP for CSF analysis: lymphocytic pleocytosis common in viral etiologies (see "Typical CSF Findings in Meningitis" table)
- Consider CSF cytology and MRI brain/spine to evaluate for malignancy
- Consider serum autoimmune and serum viral testing in appropriate settings if CSF is unrevealing and there is no improvement with empiric treatment

Empiric treatment

- Suspected bacterial meningitis: see "Empiric Treatment of Bacterial Meningitis" table
- Suspected viral meningitis: if concern for HSV meningoencephalitis → IV acyclovir
- Unclear etiology: consider initiation of empiric bacterial meningitis treatment while observing and awaiting CSF studies

Encephalitis (*NEJM* 2018;379:557)

Definition

- Inflammation of brain parenchyma characterized by impaired cerebral function (ΔMS, neurologic deficits) often due to primary viral infection or postviral inflammation

Etiologies (specific etiology found in <20% of cases; *Neurology* 2006;66:75; *CID* 2008;47:303)

- **HSV-1** all ages/seasons. If sxs recur after Rx, consider viral relapse vs. autoimmune encephalitis b/c high rates of autoimmune disease wks later (*Lancet Neurol* 2018;17:760).
- **VZV** 1° or reactivation; ± vesicular rash; all ages (favors elderly), all seasons
- **Arboviruses:** evaluate for exposure to vector/geography. Mosquitoes: **West Nile**, Eastern/Western equine, St. Louis, La Crosse; Ixodes tick: Powassan.
- Enteroviruses (coxsackie, echo): preceding URI/GI sx; peaks in late summer/early fall
- Other infectious: CMV, EBV, HIV, JC, measles, mumps, rabies, adeno, influenza, Lyme, *Ehrlichia*, RMSF, *Anaplasma*
- Noninfectious: autoimmune/paraneoplastic (anti-NMDAR, anti-Hu, anti-Ma2, anti-CRMP5, anti-mGluR5), post-infxn demyelination (eg, ADEM)

Clinical manifestations

- **Fever** + Δ**MS** (subtle to severe), seizure, focal neuro deficit, HA in meningoencephalitis

Diagnostic studies (*CID* 2013;57:1114)

- CSF analysis: **lymphocytic pleocytosis**; PCR for HSV (95% Se & Sp), VZV; consider other PCR if + epi (CMV/EBV, HIV, JC, adeno/enterovirus, WNV, *Ehrlichia*), tick serology
- Consider testing for autoimmune etiologies and serologic viral testing in appropriate settings if CSF is unrevealing and there is no improvement with empiric HSV/VZV Rx
- **MRI** (CT if unavailable); HSV temporal lobe; W. Nile & Powassan thalamic hyperintensity
- EEG to r/o seizure; findings in encephalitis are nonspecific (temporal lobe focus in HSV)

Treatment (*CID* 2023;77:e14)

- HSV/VZV: acyclovir 10 mg/kg IV q8h; *Ehrlichia*/*Rickettsia*: doxycycline if right epidemiology

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Bell's Palsy

Definition & clinical manifestations

- Acute idiopathic unilat. **facial nerve palsy** (CN VII), often presumed HSV reactivation
- P/w unilateral facial muscle weakness, hyperacusis, ↓ taste, lacrimation, & salivation
- Risk factors: pregnancy (preeclampsia), obesity, HTN, diabetes, preceding URI

Diagnosis (*Otol Head Neck Surg* 2013;149:656)

- Labs, imaging, EMG not needed in routine cases
- Ddx: Bilateral: Lyme, GBS, sarcoid. Additional neuro sx: stroke, tumor. Rash: herpes zoster. Other: otitis media, HIV, Sjögren, syphilis.

Treatment and prognosis (*CMAJ* 2014;186:917)

- 70% recover spontaneously w/in 6 mos, >80% recover with glucocorticoid treatment
- Oral corticosteroids started w/in 72 hrs of sx onset improve odds of recovery; dose varies based on severity (House–Brackmann grading). No conclusive data on antivirals.
- If eyelid closure is compromised, eye protection is crucial to prevent trauma

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Herpes Zoster (Shingles)

Definition & etiology

- Painful vesicular rash in a peripheral nerve distribution due to reactivation of VZV
- Spread by contact with active lesion (prior to crusting) in uncomplicated zoster or via airborne transmission in disseminated zoster

Clinical manifestations & complications

- **Uncomplicated**: pain in a dermatomal distribution → dermatomal eruption of erythematous papules → vesicles → crusted plaques in varying stages of evolution
- **Disseminated**: vesicles across multiple dermatomes, visceral organ involvement (pneumonia, hepatitis, CNS) seen in immunosupp. (eg, transplant, malignancy)
- **Zoster ophthalmicus**: ocular involvement (V1 of CN V) requires ***urgent ophtho eval***
- Post-herpetic neuralgia: neuropathic pain lasting >90 d after dx

Diagnosis

- Clinical diagnosis if uncomplicated. Confirm with PCR (most sensitive), DFA, and viral culture (allows for resistance testing) of vesicular fluid (scrape from unroofed vesicle).

Treatment & prevention

- Uncomplicated: acyclovir, valacyclovir, or famciclovir × 7 d; initiate w/in 72 h of onset for greatest benefit; consider after 72 h if new lesions present; minimal benefit after crusting
- Superimposed bacterial cellulitis is common; if suspected, treat with appropriate antibiotics
- Disseminated/immunosupp.: IV acyclovir, eval for visceral spread, droplet precautions
- Prevention: Shingrix (2 doses) for all Pts >50 or immunosupp. adult ≥19 yrs

BACTEREMIA & ENDOCARDITIS

BACTEREMIA

Definitions

- 1° bacteremia: bloodstream infection due to direct inoculation of the blood
- Central line–associated bloodstream infection (CLABSI): bacteremia in which the same organism is growing from peripheral and catheter cultures (*CID* 2009;49:1)
- 2° bacteremia: infection of another site (eg, UTI, PNA, colitis, etc.) spreading to blood
- Contaminant: bacteria growing in a blood culture that does not represent a true infection

Risk factors for bloodstream infections (*JAMA* 2012;308:502)

- Syndromes with high likelihood of bacteremia:
  - Sepsis
  - Endovascular infxns: endocarditis, infection of pacemaker, vascular graft or IV catheter
  - Vertebral osteomyelitis, epidural abscess, septic arthritis
- Risk factors: indwelling lines, IVDU, immunosupp. (neutropenic, transplant)
- Organisms
  - **More likely pathogenic**: *S. aureus*, β-hemolytic strep, enterococci, GNR, *S. pneumo, Neisseria, Candida*
  - **Less likely pathogenic**: coag-neg staph, diphtheroids, *Cutibacterium*
- Time to growth: <24 h → higher risk, >72 h → lower risk (except slow-growing, eg, HACEK)
- **Factors increasing likelihood of endocarditis:** high-grade bacteremia w/o source, persisting after line removal or drainage of focal source, in hosts at risk for endocarditis or w/ organisms

known to cause IE; emboli; presence of prosthetic heart valve

Diagnosis

- ≥2 sets BCx prior to abx (set = aerobic + anaerobic cx) at separate puncture sites
- If proven bacteremia, daily surveillance cxs until 48 hrs of ⊖ cxs. May not need for GNRs and clinically improving (*CID* 2017;65:1776).
- TTE/TEE if concern for endocarditis (vide infra)
- TTE and urgent ophthalmology evaluation if *Candida* is growing in BCx

Treatment (*CID* 2009;49:1; *JAMA* 2020;323:2160; *NEJM* 2025;392:1065)

- Empiric abx based on Gram stain, cx, & clinical syndrome, then tailor based on sensi

Short-Term Central Venous Catheter–Related Bloodstream Infxns	
S. aureus	Risk of endocarditis in bacteremia: ~25% (*JACC* 1997;30:1072). ID consult a/w ↓ mortality (*CID* 2015;60:1451). Remove CVC, evaluate for endocarditis, osteo, hardware infections. Abx: *MSSA* → nafcillin, oxacillin, or cefazolin. *MRSA* → vanco. 2 wks if nl host, no implants, no e/o endocarditis or metastatic infxn, o/w 4–6 wks.
Coag-neg staphylococci	CVC retention does not ↓ rate of resolution, but a/w ↑ rate of recurrence (*CID* 2009;49:1187). If CVC left, treat 10–14 d; if removed 5–7 d.
Enterococcus	Remove CVC & treat for 7–14 d
GNR	Remove CVC esp. if *Pseudomonas.* Rx for 14 d (7 if uncomplicated).
Candida spp.	Remove CVC & treat for 14 from first ⊖ BCx. ID consult a/w ↓ mortality.

- **Persistently ⊕ BCx:** remove CVCs, look for metastatic infxn (endocarditis, septic arthritis, osteo), infected thrombosis, or prosthetic material (vascular graft, PPM)

Bacterial Endocarditis (*Lancet* 2024;404:377)

Definition

- Infection of endothelium of heart (including but not limited to the valves) including both prosthetic valve endocarditis (PVE) and native valve endocarditis (NVE)

Risk factors

- **Abnormal valve** (*JAMA* 1997;277:1794; *JACC* 2018;72:2443)
  - *High risk:* prior endocarditis, prosthetic valve or ring, some congenital heart disease (unrepaired cyanotic; shunt/conduit; prosthesis in past 6 mos), transplant heart, valvulopathy, VAD
  - *Medium risk:* previous rheumatic fever, non-rheumatic valve disease (including MVP w/ MR or thickened leaflet), HCM, bicuspid AoV
- **Cardiac implantable electronic devices**
- **Risk of bacteremia:** injection drug use, indwelling central venous catheters, hemodialysis, poor dentition
- **Other risk factors:** advanced age, corticosteroid use, poorly controlled diabetes, chronic liver disease, malignancy, immunocompromised state (including HIV)

Microbiology of Endocarditis				
	Native Valve (NVE)		Prosthetic Valve (PVE)	
Etiology	**Non-IVDU**	**IVDU**	**Early** (≤60 d)	**Late** (>60 d)
Viridans Strep	**36%**	**13%**	<5%	**20%**
Enterococcus	**11%**	5%	8%	13%
S. aureus	**28%**	**68%**	**36%**	**20%**
S. epidermidis	**9%**	<5%	**17%**	**20%**
GNR	<5%	<5%	**6%**	<5%
Other	<5%	<5%	10%	10%
Fungal[a]	1%	1%	9%	3%
Culture ⊖[b]	11%	<5%	17%	12%

[a]↑ risk w/ DM, indwelling lines, immunosupp. [b]Cx ⊖ = abiotrophic strep, HACEK (*Haemophilus parainfluenzae & aphrophilus, Aggregatibacter, Cardiobacterium, Eikenella, and Kingella*), *T. whipplei, Bartonella, Coxiella, Chlamydia, Legionella, Brucella* (*JAHA* 2025;14:e040218).

Clinical manifestation

- **Persistent bacteremia → fever** (80–90%), rigors, night sweats, anorexia, myalgias
- **Valvular or perivalvular infxn → new regurgitant lesion**, **HF**, conduction abnl (eg, AVB)
- **Septic emboli**: stroke, embolic MI, renal/splenic/pulmonary infarcts, septic arthritis, osteo
- Immune complex phenomena: arthritis, glomerulonephritis
- **Subacute endocarditis**: indolent, progressive "B" sx (fatigue, wt loss), anemia (ACD)

Physical exam

- **Cardiac murmur** (85%), s/s of new HF (pulmonary edema, JVP elevation, edema)
- Skin/ocular changes (uncommon but highly specific)
  - Janeway lesions: painless hemorrhagic macules on palms/ soles due to septic emboli
  - Osler's nodes: painful nodules on pads of digits due to immune complex deposition
  - Splinter hemorrhages in proximal parts of fingernails or toenails
  - Roth spots: retinal hemorrhages
- MSK: point tenderness along spine, red/hot joints
- Neurologic deficits c/f embolic stroke; vertebral tenderness c/f osteo or epidural abscess
- Devices: evaluate CVCs, PM/ICD pocket, and sites of other hardware/prosthetics

Diagnosis (*CID* 2010;51:131; *EHJ* 2015;36:3075; *Circ* 2015;132:1435)

- **Blood cultures**: 3 sets (aerobic & anaerobic bottles) from different sites, ideally spaced ≥1 h apart and ideally before abx. ⊖ BCx (at least 2 sets) after appropriate abx have been initiated to document clearance; repeat q24–48h until ⊖.
- Serial **ECGs** to assess for conduction disease and ↑ PR interval (c/f perivalvular abscess)
- **Echocardiogram:** TTE in all Pts. **TEE** if (i) TTE abnl but nondx, (ii) TTE ⊖ but high suspicion, (iii) complications suspected or present (eg, AVB), (iv) high risk (prosthetic valve, CIED, prior IE, congenital heart dis.), (v) *S. aureus*, enterococcus, or fungus, (vi) Δ in signs or sx (eg, new conduction abnl, regurgitation, etc.), (vii) if considering a shortened course (10–14 d) of abx (vide infra).

	Sensitivity		
	NVE	**PVE**	**Abscess**

Transthoracic (TTE)	39–58%	33%	18–63%
Transesophageal (TEE)	>90%	86%	76–100%

(*Mayo Clin Proc* 2014;89:799; *Circ* 2015;132:1435; *Eur Radiol* 2015;25:2125; *J Am Soc Echo* 2016;29:315)

- **Gated Cardiac CT** useful for equivocal TTE/TEE findings or suspected paravalvular abscess. Provides better visualization than TTE/TEE of mechanical prosthesis due to less acoustic shadowing (especially for aortic). Also provides assessment of CAD, particularly useful in aortic valve IE given risk of embolization w/ cardiac catheterization.
- **PET/CT** using radiolabeled glucose (FDG) useful for suspected prosthetic valve or CIED-related endocarditis where TTE/TEE may be indeterminate or in cases of "possible IE." Including a ⊕ PET/CT scan as major criterion in Modified Duke Criteria recategorizes 76% of Pts with PVE from "possible" IE to "definite" IE (*JACC* 2013;61:2374).
- Brain/spine imaging if concern (severe HA, neuro deficit, meningeal signs) for CNS spread (mycotic aneurysms, embolic stroke) or spinal involvement (vertebral osteo, epidural abscess)
- **Cx ⊖ endocarditis:** may be due to abx prior to BCx. PCR, bacterial 16S ribosomal RNA, serol. may be helpful. Detailed hx: animal exposure (cats), travel, unpast. dairy, etc. ID eval. Consider organisms listed in cx ⊖ footnote in microbiology table (vide supra).

Modified Duke Criteria (*CID* 2023;77:518)	
Definitive: 2 major *or* 1 major + 3 minor *or* 5 minor; **Possible**: 1 major + 1 minor *or* 3 minor	
Major	**Minor**
• **Microbiologic** ⊕ **BCx** w/ common endocarditis pathogen (grown in ≥2 separate sets for typical organisms; ≥3 for non-typical) ⊕ *Coxiella, Bartonella, or Tropheryma lab* • **Imaging** echo or CT w/ vegetation, abscess, or prosthetic dehiscence new valvular regurg (worsening not suffic) FDG-PET w/ abnl metabolic activity • **Surgical:** evidence from direct inspection	• Predisposing condition (see above) • **Fever** (>38.0°C) • **Vascular phenomena:** septic arterial or pulmonary emboli, mycotic aneurysms, ICH, Janeway lesions • **Immune phenomena:** ⊕ RF, GN, Osler's nodes, Roth spots • Micro not meeting major criteria • Abnl FDG-PET w/in 3 mos of implantation of prosthetic material

Treatment (ID consult is strongly recommended)

Treatment (*Circ* 2015;132:1435)	
Empiric	NVE or PVE >12 mos post-op: vanc + CTX PVE <12 mos post-op: vanc + CTX ± gentamicin (if OK renal fxn)
Strep	Penicillin, ampicillin, CTX; consider gentamicin in discussion w/ ID
Staph (*S. aureus* and *lugdunensis*)	MRSA: vanc or dapto MSSA: nafcillin, oxacillin, or cefazolin (avoid if CNS involvement due to poor penetration); vanc inferior to β-lactam for MSSA For PCN allergy w/ MSSA consider desensitization

	Consider rifampin/gentamicin in PVE in discussion w/ ID
Enterococci	Ampicillin + [CTX or gent]; if VRE: linezolid, dapto, ampicillin if sensitive
Gram negatives	HACEK: CTX, ampicillin, or FQ. *Pseudomonas*: 2 anti-Pseudomonal agents [eg, β-lactam + (aminoglycoside or FQ)].
Fungi (*Candida*, aspergillus)	*Candida*: amphotericin B ± flucytosine or micafungin *Aspergillus*: amphotericin B or voriconazole Ophtho consult for fungemia to rule out endophthalmitis

- De-escalate abx to organism-directed therapy based on speciation and sensitivities
- If on anticoagulation or antiplatelet, typically can continue unless concern for stroke, intracranial hemorrhage, or need for emergent surgery
- Monitor for complications of endocarditis (CHF, conduction block, osteomyelitis, new embolic phenomenon) which can occur even on abx
- Duration is usually **4–6 wks**
  - After ≥10 d IV abx can consider Δ'ing to PO if clinically appropriate and available PO abx in consultation with ID (*NEJM* 2019;380:415)
  - Uncomplicated right-sided NVE or PCN-S *Strep* spp. → 2 wks may be adequate
- IVDU-associated best managed by multidisciplinary teams including Addiction Medicine

Indications for surgery (consult early; *JTCS* 2017;153:1241; *Circ* 2021;143:e72)

- Emergent if refractory cardiogenic shock
- Urgent (during initial hospitalization):
  - **Sx HF**
  - **Penetrating infection**: periannular abscess, heart block, fistula, worsening conduction
  - **Persistent infection**: ⊕ BCx after >5–7 d of appropriate abx, ↑ or ? large vegetation
  - **Emboli**: recurrent or w/ residual large (>10 mm) vegetation & severe AR/MR. Cerebral emboli *not* contraindic. unless severe stroke or hemorrhage (*Stroke* 2006;37:2094).
  - *S. aureus*, fungal or multiRx-resistant organisms
  - PVE (emergent if dysfunction or dehiscence)

Endocarditis Prophylaxis (*Circ* 2007;116:1736)	
Cardiac conditions*	**Prosthetic valve; previous endocarditis; congenital heart disease** (CHD) including unrepaired or incompletely repaired cyanotic CHD (palliative shunts or conduits), 1st 6 mo after completely repaired CHD using prosthetic material; cardiac transplant recipients w/ valvulopathy. (Prophylaxis no longer rec. in acquired valvular dysfxn, bicuspid AoV, MVP with leaflet thickening or regurgitation, HCM.)
Procedures*	**Dental:** manipulation of gingival tissue or periapical region of teeth or perf oral mucosa (eg, extraction, periodontal, implant, root canal, cleaning)
Regimens	Oral: **amoxicillin 2 g 30–60 min before.** If missed, up to 2 hrs after OK. Unable to take PO: amp 2 g IM/IV or cefazolin or CTX 1 g IM/IV PCN-allergic: cephalexin or azithro or claritho or doxy

*Pts should meet both indications (high-risk condition & high-risk procedure) to qualify for Ppx

TUBERCULOSIS

Definitions

- **Primary**: new *Mycobacterium tuberculosis* (TB) in a naïve host; sx or asx; 90% of infected normal hosts will never develop clinically evident disease
- **Latent**: well-controlled infection without clinical or radiographic evidence of active disease; can persist for years to decades
- **Reactivated**: activation of latent; more likely in the setting of immunosuppression
- **Miliary**: disseminated lympho-hematogenous spread due to primary or reactivated TB
- **Multidrug-resistant (MDR):** resistant to isoniazid (INH) & rifampin. Can occur as 1° infxn.
- **Extensively drug-resistant (XDR):** resistant to INH, rifampin (RIF), fluoroquinolones (FQ), and at least one of amikacin, kanamycin, or capreomycin

Epidemiology (*Lancet* 2025;405:850)

- Transmission via aerosols; untreated active dx requires airborne isolation in health care facilities and community isolation measures; must involve local public health authorities
- Acquisition: residents/travel in TB-endemic area, IVDU, resident/worker in correctional facility or homeless shelter, close contact w/ active TB
- Reactivation: risk is 5% in first 2 yr, 5–10% overall; ↑ if HIV ⊕, immunosupp. (anti-TNF, steroids), ESRD, DM, cancer, transplant, malnourished, smoking, substance use disorder

Screening for latent TB

- Whom to screen: high likelihood of exposure and/or high risk of progression to active disease including HIV ⊕ and prior to immunosuppression (pretransplant or anti-TNF)
- Nb, testing for host exposure & immune response to TB, ***not whether TB active*** (vide infra)
- As relies on host immune system, limited Se in immunosuppressed individuals
- Screening tests
  - IFN-γ release assays (IGRA): preferred test; Ag-stimulated IFN-γ release from Pt's T cells. ↑ Sp over TST/PPD in BCG vaccinated Pts.
  - Tuberculin skin test (TST/PPD): inject purified protein intradermally, examine for wheal 48–72 hrs later. Interpret based on max diameter of induration, not erythema.

Size of Reaction	Persons Considered to Have ⊕ Test (*NEJM* 2002;347:1860)
>5 mm	HIV ⊕ or immunosupp. (eg, prednisone 15 mg/d × >1 mo) Close contacts of Pt w/ active TB; CXR c/w prior active TB
>10 mm	All other populations with ↑ prevalence/risk. Health care workers, recent conversion (↑ induration by >10 mm in 2 y).
>15 mm	No risk factors
False ⊖	Faulty application, anergy (including from active TB), acute TB (2–10 wk to convert), acute non-TB mycobacteria (NTM), malignancy
False ⊕	Improper reading, cross-reaction with NTM, BCG vaccination (although usually <10 mm by adulthood)
Booster effect	↑ in duration b/c immunologic boost by prior skin test in prev sensitized individual (by TB, NTM, or BCG). Test ⊖ → ⊕ but *not* true conversion due to *recent* infxn. 2nd test true baseline. Can be 1 y after initial test.

Clinical manifestations (*Lancet* 2025;405:850)

- **Constitutional symptoms are common in all manifestations, but may be absent**
- **Primary TB pneumonia:** middle or lower lobe consolidation, ± effusion, ± cavitation
- TB pleurisy: pulmonary effusion ± pericardial and peritoneal effusions secondary to granuloma breakdown and local inflammation; can occur in primary or reactivation

- **Reactivation TB pulmonary disease**: upper lobe infiltrate ± volume loss ± cavitation
- **Miliary TB**: diffuse millet seed–sized lesions, more common in immunosupp.
- Extrapulmonary TB: lymphadenitis, pericarditis, peritonitis, CNS disease including meningitis, GU tract disease ± sterile pyuria, osteoarticular disease (vertebral = Pott's disease), granulomatous hepatitis, splenitis, cutaneous disease
- TB and HIV: HIV ⊕ at ↑ risk infxn, reactivation (8–10%/yr without ART, higher w/ ↓ CD4), and progressive 1° infxn. CXR can be atypical espec. if CD4 ≤200 (*JAMA* 2005;293:2740).

Diagnostics for active TB (*CID* 2017;64:11)

- **Pulmonary TB**: common CXR findings discussed above; induced sputum **AFB smear** & **culture** (3 samples at least 8 h apart) ± NAAT/PCR (GeneXpert); consider bronchoscopy + BAL ± transbronchial biopsy. GeneXpert can also detect RIF resistance (non-bloody sputum only). Sp 98%/Se 74%, independent of HIV status.
- **Extrapulmonary TB**
  - *Pleural/pericardial effusions or ascites:* fluid sampling for AFB cx/smear, NAAT/PCR, cell counts. Adenosine deaminase (ADA) can be ↑, best validated in ascites. Free IFN-γ can be elevated in pleural/ascitic fluid (not validated in pericardial effusions). Higher diagnostic yield with pleural/pericardial biopsies for disease at these sites.
  - *CSF:* fluid sampling for AFB cx/smear (submit at least 10 mL), NAAT/PCR, cell count (lymphocyte predominance), glucose (low), protein (high), ADA (high)
  - *Soft tissue:* tissue biopsy with AFB staining, pathology w/ granulomas

Treatment of latent TB

- If screening test ⊕ and no risk factors, confirm prior to treatment; if ⊕ w/ risk factors, proceed to treatment (*CID* 2017;64:11)
- **Prior to treatment of latent TB, active TB must be ruled out** with, at a minimum, ROS for symptoms (cough, fever, night sweats, weight loss), physical exam, and CXR (though may be normal in immunosupp.). Obtain HIV screening if risk factors.

Scenario	Prophylaxis Regimen
PPD/IGRA ⊕ (regardless of HIV status)	1st line: Rifampin × 4 mo *or* INH/rifampin daily × 3 mos *or* INH/rifapentine weekly × 12 wks (*MMWR* 2020;69:1) *Alternative:* INH + vitamin B_6 × 6–9 mos
Contact case known or suspected to have MDR-TB	No proven regimen: ? PZA + EMB, ? PZA + FQ (*NEJM* 2024;391:2304)

- ✓ LFTs monthly if receiving INH (risk ↑ w/ age; *Chest* 2005;128:116): if AST/ALT ↑ 5× ULN *or* sx (nausea, vomiting, abd pain) → stop TB meds & re-eval

Patient isolation

- Decision based on likelihood of active disease. Consider when cough, dyspnea, hemoptysis, ≥1 risk factor (HIV ⊕, foreign born, substance use disorder, homeless, recent incarceration, prior TB or exposure).
- Discontinue if alternative dx and AFB smear neg ×3, or TB treated for 2 wk & AFB neg ×3

Treatment of active tuberculosis (*Lancet* 2025;405:850)

- Prior to treatment, **consult ID**, check LFTs, Cr, **HIV** & hepatitis A/B/C screen, DM screen, pregnancy screen, vision testing for acuity and color, EtOH use history
- **CNS TB**: consider steroids, optimal regimens & dosing for CNS penetration w/ ID consult
- Treatment requires several drugs to prevent resistance (vide infra)

- **Suspect MDR-TB** if prior TB Rx (esp. if poor adherence), travel to area w/ ↑ rates of MDR (India, China, Eastern Europe including Russia, South Africa), exposure to person w/ likely MDR-TB (*NEJM* 2008;359:636)
- "Paradoxical *worsening*" of sx can occur after starting Rx. More common w/ extrapulm. TB & more frequent/severe w/ concurrent immune reconstitution (eg, HIV ⊕ Pts started on ART, Pts taken off immunosuppression). **Must r/o Rx failure** (repeat cx, imaging), consider checking drug levels.
- Duration of treatment varies based on host, clinical manifestation, and improvement/ progression on treatment

Antituberculous Medications	
Drug	**Adverse Effects***
Isoniazid (INH)	Hepatitis (avoid EtOH), periph neuropathy (↓ risk by suppl. vit B_6), drug-induced lupus
Rifampin (RIF)	Orange tint of body fluids, GI upset, hepatitis (avoid EtOH), hypersensitivity, fever, drug interaction, thrombocytopenia
Pyrazinamide (PZA)	Hepatitis (avoid EtOH), hyperuricemia, arthritis
Ethambutol (EMB)	Optic neuritis
Streptomycin (SM)	Ototoxicity, nephrotoxicity
Amikacin (AMK)	Ototoxicity, nephrotoxicity
Quinolone (moxifloxacin, levofloxacin)	GI upset, tendinopathy, ↑ QTc

*Risk of hepatitis ↑ w/ preexisting liver disease. Consult ID, consider holding/replacing PZA or INH.

Scenario	Antituberculous Treatment Regimens
Pulmonary TB **≥4% INH-resist. in community** (incl. most of U.S.)	INH + RIF + PZA + EMB until suscept. known If *sensitive* to INH & RIF → INH + RIF + PZA × 2 mo, *then* → INH + RIF × at least 4 mo If *resistant*, see next row
Drug-resistant TB (INH-R, RIF-R, or MDR/XDR)	*Consult ID specialist* (*NEJM* 2008;359:636 & 2025;392:468)
Extrapulmonary TB	*Consult ID specialist*
TB in HIV ⊕ patient	*Consult ID specialist*

HIV/AIDS

Definition & clinical manifestations

- Acute HIV: rash, lymphadenopathy, fever, oral ulcers, pharyngitis, myalgias, diarrhea Presents ~2–6 wk after exposure; not all HIV infections result in symptoms of acute HIV
- AIDS: HIV + CD4 <200/mm^3 *or* AIDS-defining opportunistic infection (OI) or malignancy

Epidemiology

- ~1.2 million Americans living w/ HIV (13% unaware); ~40 million worldwide
- **High-risk groups:** MSM, transgender women, IVDU, sex worker, partners of high-risk Pts
- Transmission: sexual (risk 0.1–1% per sex act w/o ARV), needlesticks (occupational or IVDU), vertical (15–40% w/o ARV), transfusions, organ transplant (uncommon in U.S.)

Prophylaxis (*J Infect Dis* 2018;218:16; *JAMA* 2023;330:746; cdc.gov/hivnexus/hcp/prep)

- **Preexposure** (PrEP): TDF/FTC qd or on-demand, TAF/FTC qd, or CAB IM q2mo (regimen depends on gender identity); ↓ transmission >90% if adherent. Consider in high-risk groups, STI w/in 6 mo, IVDU, or anyone who asks for it. **R/o HIV before initiation**, ✓ HBV status, renal fxn, STIs, & HIV at start. HIV Ag/Ab + VL q3mo. Renal fxn q12mo.
- **Postexposure** (PEP): start ASAP (w/in 72 hr) after high-risk, blood-borne, or mucosal bodily fluid exposure if source HIV+. In exposed, ✓ baseline HIV, STIs, HBV, HCV, renal fxn, LFTs, hCG. Rx: TDF/FTC + DTG or RAL × 28 days. ✓ drug-drug interactions.

Screening and diagnosis (*JAMA* 2018;320:379)

- Screen all 13–64 yo at least once, every preg, if new STI dx; **screen high risk annually**
- **HIV Ab/p24Ag** (ELISA assay): ⊕ 1–12 wk after acute infxn; >99% Se; 1° screening test
- If ⊕, Ab differentiation assay confirms and differentiates HIV-1 vs. -2
- **HIV RNA PCR viral load (VL)** in plasma; assay range is 20–10 million copies/mL; false ⊕ can occur, but usually low # copies; in contrast, VL should be high (>750 k) in 1° infxn
- **CD4 count:** not a dx test, b/c can be HIV ⊕ w/ normal CD4 or be HIV ⊖ w/ low CD4

Approach to newly diagnosed HIV ⊕ Pt (*CID* 2020;73:e3572; *JAMA* 2025;333:609)

- Counsel re: excellent prognosis w/ adherence to treatment, treatment options, & disclosure
- **Lab eval:** CD4, HIV VL & genotype, CBC w/ diff., BMP, LFTs, HbA1c, lipids, UA, PPD/ IGRA, syphilis, *Chlam.* & gonorrhea (3 site), Hep A/B/C, anal PAP if MSM or transgender ♀ >35, hCG, HLA-B*5701 if Rx w/ abacavir planned. If AIDS: CMV IgG, Toxo IgG, G6PD.
- Confirm all vaccinations (including annual flu) are up to date, avoid live vax if CD4 ≤200
- **Initiate ARV early** (same day, preferably after labs/genotype and w/ *guidance from HIV specialist*) regardless of CD4 level because ↓ mortality (*NEJM* 2015;373:795)
- **Rx prevents transmission to partners.** Risk of transmission w/ unprotected sex is ~0% (untransmissible) if VL undetectable >6 mo (*JAMA* 2016;316:171; *Lancet* HIV 2018;5:e438).
- Regimens incl.: 2 NRTI (eg, TXF+FTC) + *either* INSTI (eg, BIC) *or* boosted PI (eg, DRV/r)

Common Antiretrovirals (ARVs)		**Common Side Effects**
NRTI	abacavir (ABC; Ziagen) emtricitabine (FTC; Emtriva) lamivudine (3TC; Epivir) tenofovir (TAF or TDF) zidovudine (AZT; Retrovir)	*Class:* GI intol, lipoatrophy, lactic acidosis ABC: hypersensitivity (3%), ✓ **HLA-B*5701** AZT: BM suppression (esp. macrocytic anemia) TDF: renal toxicity, bone density loss TAF: minimal renal toxicity
NNRTI	efavirenz (EFV; Sustiva) etravirine (ETR; Intelence) nevirapine (NVP; Viramune) rilpivirine (RPV; Edurant)	*Class:* rash, hepatitis, mixed CYP450 inducer/inhib EFV: CNS effects (incl depression) NVP: rash and hypersensitivity [risk factors are female, CD4 >250, pregnancy (∴ avoid)]
PI	atazanavir (ATV; Reyataz)	*Class:* GI intol; hepatotoxicity; inhibit CYP450 (many DDIs, eg, statins, steroids, DOACs); ↑ glc; hyperlipid (less w/ ATV); MI (*NEJM* 2007;356:1723)

	darunavir (DRV; Prezista) *PIs given w/ boosters ritonavir or cobicistat for ↑ PK*	ATV: crystalluria → nephrolithiasis DRV: rash (10%); possible sulfa cross-reactivity
EI	maraviroc (MVC; Selzentry)	Dizziness, hepatotoxicity; ✓ CCR5 tropism assay
INSTI	bictegravir (BIC; Biktarvy) dolutegravir (DTG; Tivicay) elvitegravir (EVG; Vitekta) raltegravir (RAL; Isentress) cabotegravir (CAB; Vocabria)	Class: diarrhea; weight gain; ↑ CPK DTG/BIC ↑ metformin levels; monitor glc CAB/RPV: injection site rxn

NRTI, nucleoside/tide reverse transcriptase inhib; NNRTI, nonnucleoside RTI; PI, protease inhib; EI, entry inhib (CCR5 antagonist); INSTI, integrase inhib; several multiclass combo pills exist

- Initiation of ARVs may *transiently worsen* existing OIs (TB, MAC, CMV, others) due to immune reconstitution inflammatory syndrome (IRIS). Prednisone during 1st 4 wks of ARVs ↓ risk for TB-associated IRIS, but not routinely given (*NEJM* 2018;379:1915).
- **Do not start ARVs** immediately if c/f cryptococcal or TB meningitis
- After start, ✓ VL q4wk until UD, then q3mo. Q6mo if UD >1 yr and clinically stable.

Approach to previously established HIV ⊕ Pt

- H&P (mucocutaneous, neurocognitive, OIs, malignancies, STDs); meds and adherence
- Review ARVs (past and current); if hospitalized typically continue ARVs, if any must be held, *stop all* to ↓ risk of resistance
- Regimen failure: cannot achieve undetectable VL after months on ARVs, viral rebound (VL >200 copies/mL ×2 after prior suppression), ↓ CD4 count or clinical worsening

OI Prophylaxis (*JAMA* 2018;320:379; clinicalinfo.hiv.gov)		
OI	**Indication**	**1° Prophylaxis**
Tuberculosis	⊕ PPD (≥5 mm), IGRA, *or* high-risk exposure	See treatment for latent TB
Pneumocystis jirovecii (PCP)	CD4 <200/mm *or* CD4 <14% or thrush	TMP–SMX DS qd (first line) *or* dapsone qd *or* atovaquone qd *or* pentamidine inhaled q4wk
Histoplasmosis	CD4 <150/mm + endemic/exposure	Itraconazole qd
Toxoplasmosis	CD4 <100/mm^3 *and* ⊕ *Toxo* IgG	TMP–SMX DS qd *or* dapsone 50 mg qd + pyrimeth. qwk + leucovorin 25 qwk
MAC	Ppx no longer rec. if effective ARVs initiated	
When to stop Ppx: PCP and toxo if CD4 >200 × 3 mos (or CD4 >100 and HIV VL undetectable × 3–6 mos); Histo if CD4 >150 × 6 mos and HIV VL undetectable		

Complications of HIV/AIDS

CD4	Complications

Count	
Any	*S. pneumo*, TB, VZV, HPV complications, Kaposi's sarcoma, lymphoma, ↑ CVD risk, ↓ bone density
<500	Constitutional sx. Mucocutaneous: seborrheic dermatitis; psoriasis; oral hairy leukoplakia; HSV. Recurrent bacterial infxns.
<200	PCP*, Toxo,* PML*, Crypto, Candida, Histo/Coccidio* (endemic areas)
<50–100	CMV, MAC, CNS lymphoma, invasive aspergillosis, bacillary angiomatosis (dissem. *Bartonella*), death (<50 is medical emergency)

Fever workup in patient with HIV/AIDS

- Etiologies (*Infect Dis Clin North Am* 2007;21:1013)
  infxn (82–90%): MAC, TB, CMV, early PCP, *Histo*, *Crypto*, *Coccidio*, *Toxo*, endocarditis
  noninfectious: lymphoma, drug reaction. Non 1° HIV itself rarely (<5%) cause of fever.
- Workup: guided by CD4 count, clinical syndrome, epi, & exposures
  CBC, BMP, LFTs, BCx, CXR, UA, mycobact. & fungal cx, ✓ meds, ✓ chest & abd CT
  CD4 <100–200 → serum crypto Ag, urinary *Histo* Ag, CMV PCR
  pulmonary s/s → CXR; ABG; sputum for bacterial cx, PCP stain, AFB; bronchoscopy
  diarrhea → stool cx/PCR, O&P, AFB; direct visualization with bx on colonoscopy
  cytopenias → BM bx for path & cx of aspirate including for mycobacteria & fungi
  headache/visual Δs→ LP; CSF for bacterial/fungal/mycobacterial cx, CrAg, MTb PCR, Toxo PCR; JCV PCR; CMV PCR from serum; MRI brain; dilated eye exam w/ Ophtho

Cutaneous

- Eosinophilic folliculitis; **warts** (HPV); HSV & VZV; MRSA SSTI; scabies; candidiasis; eczema; prurigo nodularis; psoriasis; drug eruption; subungual onychomycosis
- Molluscum contagiosum (poxvirus): 2–5 mm pearly papules w/ central umbilication
- **Kaposi's sarcoma** (KSHV or HHV-8): red-purple nonblanching nodular lesions
- Bacillary angiomatosis (disseminated *Bartonella*): friable violaceous vascular papules

Oral

- Aphthous ulcers; KS; **thrush/oral candidiasis** (curd-like patches + odynophagia)
- Oral hairy leukoplakia**:** painless proliferation of papillae w/ adherent white coating usually on lateral tongue, caused by EBV but not precancerous

Ophthalmologic

- **CMV retinitis** (CD4 often <50); Rx: ganciclovir or valganciclovir, foscarnet, or cidofovir
- HZV, VZV, syphilis (any CD4 count, *treat as neurosyphilis*), or *Toxo* (CD4 usually <100)

Endocrine/metabolic

- Hypogonadism; adrenal insufficiency (CMV, MAC, TB, HIV, or med-related); sarcopenia; osteopenia/porosis/fragility fractures (at all CD4 counts)
- **Lipodystrophy**: central obesity, peripheral lipoatrophy, dyslipidemia, hyperglycemia

Cardiovascular (*JACC* 2013;61:511)

- Higher rates of CAD, stroke, VTE, dilated CMP; pulm. HTN; pericarditis/effusion

Pulmonary

Radiographic Pattern	Common Causes
Normal	Early PCP
Diffuse interstitial infiltrates	PCP, TB, viral, or disseminated fungal
Focal consolidation or masses	Bacterial or fungal, TB, KS
Cavitary lesions	TB, NTM, aspergillus, other fungal, bacterial (incl. *Staph aureus*, *Nocardia, Rhodococcus*)
Pleural effusion	TB, bacterial or fungal, KS, lymphoma

- ***Pneumocystis jirovecii* (PCP) pneumonia** (usually CD4 <200)
  fever, night sweats, dyspnea on exertion, dry ("doorstop") cough
  CXR w/ interstitial pattern, ↓ P_aO_2, ↑ A-a ∇, ↑ LDH, ⊕ PCP sputum stain, ⊕ **β-glucan**
  Rx if P_aO_2 >70: TMP-SMX 15–20 mg of TMP/kg divided tid, avg dose = DS 2 tabs PO tid
  Rx if P_aO_2 <70 or A-a gradient >35: prednisone before abx (40 mg PO bid; ↓ after 5 d)

Gastrointestinal & hepatobiliary

- Esophagitis: *Candida*, CMV (solitary, serpiginous), HSV (multiple, small shallow), giant aphthous ulcers, pills; EGD if no thrush or no response to empiric antifungals
- Enterocolitis: *bacterial* (esp. if acute: *Shigella*, *Salmonella*, *C. diff*); *protozoal* (esp. if chronic: *Giardia*, *Cystoisospora*, *Cryptosporidium*, *Cyclospora*, Microsporidia, *Entamoeba*); *viral* (CMV, adeno); *fungal* (histo); MAC; AIDS enteropathy; TB enteritis
- GIB: CMV, KS, lymphoma, histo; Proctitis: syphilis, HSV, CMV, *LGV, N. gonorrhoeae*
- Hepatitis: HBV, HCV, CMV, MAC, TB, histo, syphilis, drug-induced
- AIDS cholangiopathy: often a/w CMV or *Cryptosporidium or* Microsporidia (at ↓ CD4)

Renal

- HIV-assoc. nephropathy (collapsing FSGS); **nephrotoxic drugs** (eg, TDF → prox tub dysfxn)

Hematologic/oncologic (*NEJM* 2018;378:1029)

- Cytopenia: ACD, BM infiltration by tumor/infxn (eg, MAC/TB), drug toxicity, hemolysis, ITP
- Non-Hodgkin lymphoma: ↑ frequency with any CD4 count, but incidence ↑ with ↓ CD4
- Hodgkin lymphoma (any CD4; impact of ARVs unclear)
- CNS lymphoma: CD4 count <50, EBV-associated
- **Kaposi's sarcoma** (HHV-8): at any CD4 count, incidence ↑ b/c CD4 ↓, usu. MSM *Mucocut.* (violaceous lesions); *pulmonary* (nodules, infiltrates, LAN); *GI* (bleed, obstruct.)
- Cervical/anal CA (HPV high risk in MSM, transgender women)
- ↑ rates of liver CA (a/w HBV/HCV), gastric CA

Neurologic/psychologic

- **Meningitis**: *Crypto* (dx w/ CSF; serum CrAg 90% Se), bacterial (inc. *Listeria*), viral (HSV, CMV, 1° HIV), TB, histo, *Coccidio*, lymphoma; neurosyphilis (cranial nerve palsies)
- **Space-occupying lesions**: may present as HA, focal deficits or ΔMS. Workup: MRI, brain bx only if suspect non-*Toxo* etiology (*Toxo* sero ⊖) or no response to 2 wk of empiric anti-*Toxo* Rx (if *Toxo*, 50% respond by d3, 91% by d14; *NEJM* 1993;329:995).

Etiology	Imaging Appearance	Diagnostic Studies
Toxoplasmosis	Enhancing lesions, typically in basal	⊕ *Toxo* serology (Se >95%),

	ganglia (can be multiple)	CNS PCR (~60% Se)
CNS lymphoma	Enhancing ring lesion (single 60% of the time)	⊕ CSF PCR for EBV ⊕ SPECT or PET scan
Progressive multifocal leukoencephalopathy (PML)	Multiple nonenhancing lesions in white matter	⊕ CSF PCR for JC virus
Other: abscess, nocardiosis, crypto, TB, CMV, HIV	Variable	Biopsy

- HIV-assoc. dementia: depressive sx, impaired attention/concentration, psychomotor slowing
- Depression: ↑ rates of suicide/depression
- Myelopathy: infxn (CMV, HSV), cord compression (epidural abscess, lymphoma)
- Peripheral neuropathy: meds (esp 1st-gen NRTIs), CMV, diabetes

Disseminated *Mycobacterium avium* complex (DMAC)

- Fever, night sweats, wt loss, abd pain, diarrhea, pancytopenia. Can cause localized lymphadenitis. Rx: clarithro/azithro + ethambutol. If severe, consider rifamycin.

Cytomegalovirus (CMV)

- Retinitis, esophagitis, colitis, hepatitis, neuropathies, encephalitis. CMV VL may be ⊖. Consider tissue biopsy. Rx: ganciclovir, valganciclovir, foscarnet, or cidofovir.

TICK-BORNE DISEASES

Distinguishing Features of Tick-Borne Illnesses

Disease	Rash	↓ WBC	Anemia	↓ Plts	↑ LFTs
Lyme	80%: erythema migrans	–	–	–	+
RMSF	90%: petechiae, palms/soles (can be absent initially)	–	+	+	+++
Borrelia miyamotoi	–	++	+	+++	+++
Ehrlichia	25%: maculopap, petechiae	+++	++	++++	++++
Anaplasma	–	+++	+	+++	++++
Babesia	–	+	++++ (lysis)	++++	+++

–: <15%, +: 15–25%, ++: 25–50%, +++: 50–75%, ++++: >75%

Tick prophylaxis: protective clothing, tick ✓ q24h, DEET/picaridin, if bitten remove ASAP

Lyme Disease

Microbiology & epidemiology

- Spirochete *B. burgdorferi* transmitted by *Ixodes scapularis* (deer tick)
- Ticks in low brush near wooded areas (high tick risk: low brush, leaf litter, tall grass)
- Infection usually requires tick attached >36–48 h

- Most common vector-borne illness in U.S.; peak in summer in NE/Mid-Atlantic/Midwest
- Consider coinfection w/ *Anaplasma*, *Babesia, B. miyamotoi*

Clinical Manifestations (*NEJM* 2014;370:1724; *CID* 2020;72:e1)	
Stage	**Manifestations**
Early localized (w/in 1 month)	*General:* flu-like illness. *Derm* (~80%): **erythema migrans** (EM) = erythematous patch ± central clearing, ~6–38 cm.
Early disseminated (wks to mos)	*General:* fatigue, malaise, LAN, HA *Derm:* multiple EM lesions *Rheum* (~10%): migratory arthralgias & myalgias *Neurologic* (~15%): cranial neuropathies (esp. CN VII), aseptic meningitis, mononeuritis multiplex (± pain), transverse myelitis *Cardiac* (~8%): heart block, myopericarditis
Late disseminated (mos to yrs)	*Derm* (rare in U.S.): acrodermatitis chronica atrophicans, panniculitis *Rheum* (~60%, espec. if not Rx'd): recurrent mono- or oligoarthritis of large joints (classically knee), synovitis *Neurologic* (rare!): subacute encephalomyelitis, polyneuropathy

Diagnostic studies (*CID* 2020;72:e1)

- Avoid testing without signs/symptoms
- *Early localized:* clinical dx if EM + possible exposure; no need for testing (often sero ⊖)
- *Early or late disseminated:* 2-step testing
  - 1st step: ELISA screen (some false ⊕, false ⊖ w/ early abx or <6 wk after tick bite)
  - 2nd step: if ⊕ ELISA, confirm with IgM/IgG Western blot (↑ Sp) or 2nd ELISA
- Serum testing is sufficient for diagnosis of Lyme CNS infection or Lyme arthritis, though consider CSF (Ab testing in parallel with serum) or joint fluid sampling (PCR) to rule out other causes and provide a more definitive diagnosis

Treatment (*CID* 2021;72:e1)

- **Prophylaxis**: doxycycline × 1 *only* if *all* of the following:
  1. *Ixodes scapularis* tick attached ≥36 h
  2. Local Lyme carriage in ticks ≥20%
  3. Abx can be given w/in ≤72 h of tick bite
  4. No contraindication to doxycycline (eg, preg, allergy, age <8 y)

  Regardless of Ppx, monitor for fever, flu-like sx, rash (erythema migrans) × 30 d
- **Treatment**

  Isolated EM: doxy × 10 d (alternative: cefurox or amox × 14 d or azithro × 7 d)

  Arthritis: doxy × 28 d (or cefurox or amox × 28 d). Doxy-refractory: repeat doxy or 2 g IV CTX × 28 d. Post-Lyme infxn autoimmune arthritis can occur; Rheum referral for Rx.

  Carditis/meningitis: CTX IV or doxy PO (based on severity/response) × 14–21 d
- Consider coinfection if severe/refractory sx, persistent fever, cytopenias
- Recurrent EM after abx are likely reinfection, *not* relapse (*NEJM* 2012;367:1883)

Babesiosis

Microbiology & epidemiology (*MMWR* 2012;61:505)

- *Babesia microti* (U.S.) transmitted by *Ixodes* ticks; also risk from blood transfusion
- Peak incidence summer in NE U.S. (esp. coastal, "Nantucket fever"), north-central Midwest

Clinical manifestations

- Typically 1–4 wks after tick exposure; <9 wks if transfusion
- Range: asx/mild flu-like sx to severe DAT ⊖ **hemolytic anemia**/DIC, multiorgan failure
- Risk factors for severe dx: **asplenia**, ↓ cellular immunity, TNF inhib, ↑ age, pregnancy

Diagnosis (*CID* 2021;72:e49)

- Symptoms + blood smear w/ intraerythrocytic parasites (ring forms)
- Degree of parasitemia = % infected RBC on smear (correlates roughly w/ severity)
- Repeat smears (q12–24h) if sx persist despite negative initial smear
- PCR serum if smear ⊖ (or unavailable) and clinical suspicion

Treatment (*CID* 2021;72:e49)

- Atovaquone & azithro preferred; clinda/quinine (more adverse events); call ID if severe
- Duration depends on host; immunosupp often need longer Rx
- If severe, call ID to consider exchange transfusion if parasitemia >10%, severe hemolysis/ end-organ failure

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Ehrlichiosis/Anaplasmosis

Microbiology & epidemiology

- Gram ⊖ obligate intracellular bacterium; **human monocytic ehrlichiosis** (*E. chaffeensis*, HME); **human granulocytic anaplasmosis** (*A. phagocytophilum*, HGA)
- Transmission: HME by *Amblyomma americanum* (lone star tick), *Dermacentor variabilis* (dog tick); HGA by *Ixodes*; **HGA** in NE, mid-Atl, MN; **HME** in SE and south-central U.S.
- Peak incidence spring and early summer; can be transmitted by blood transfusion

Clinical manifestations (typically w/in 3 wks of tick exposure)

- Asx or nonspecific: **fever**, **myalgias**, malaise, **HA**, delirium; meningoencephalitis
- Laboratory: leukopenia, thrombocytopenia, ↑ aminotransferases, ↑ LDH, ↑ CK
- Severe disease can be complicated by bacterial superinfection

Diagnosis

- Intraleukocytic morulae on peripheral smear in acute infection; serum PCR ⊕ in acute infection and convalescence

Treatment (*JAMA* 2016;315:1767)

- Start Rx based on clinical suspicion; definitive dx requires PCR (but not 100% Se)
- Doxycycline × 10 d; if Pt does not defervesce in ≤48 h, consider coinfection/alt dx

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Rocky Mountain Spotted Fever (RMSF)

Microbiology & epidemiology

- Infection with *Rickettsia rickettsii* (Gram ⊖ obligate intracellular bacterium)
- Transmitted by *D. variabilis, D. andersoni* (wood tick); peak in spring/early summer
- Occurs in mid-Atl, SE/south-central U.S., mountain west, Mexico, Central & S. America

Clinical manifestations (typically w/in **1**–2 wks of tick exposure)

- Nonspecific: **fever**, **HA**, ΔMS, myalgias, N/V, occasionally abdominal pain
- Rash (2–5 d *after* onset of fever) = *centripetal:* starts on ankles and wrists → trunk, palms, & soles; progresses from macular to maculopapular to petechial
- Severe cases → vasculitis, multiorgan failure, meningoencephalitis; more likely in elderly

Diagnosis (*MMWR* 2016;65:1)

- Clinical dx (often w/o rash initially); *requires high suspicion* given risk of delayed Rx
- Acute illness: skin bx for rickettsiae (Se 70–90%), consider ✓serologies (may be ⊖)
- Confirm dx: recheck serology 14–21 d later, ⊕ if 4-fold ↑

Treatment (*MMWR* 2016;65:1)

- Doxy × 7–10 d, empiric Rx if suspicion; if does not defervesce in ≤48 h ? coinfection/alt dx

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Tularemia

Microbiology

- Infxn w/ *Francisella tularensis* bacteria via arthropod bites, animal contact (bite, scratch, lick), contaminated food or water, aerosolized materials

Clinical manifestations (typically w/in 2–10 d of exposure)

- Fever, chills, malaise, HA, nausea, myalgias; ulcer w/ black eschar at site of entry; LAN; conjunctivitis; pharyngitis; PNA

Diagnosis & treatment

- Serology should be collected at presentation and 2 wks later, bacteria difficult to culture
- FQ for mild infection, aminoglycoside for severe infection in consultation with ID

FEVER SYNDROMES

Temperature ≥100.4°F or ≥38°C

Diagnostic approach

- Thorough history including ROS, PMH/PSH, immunizations, including from childhood
- **Fever curve** (holding antipyretics); look at trend/pattern. Less likely to mount fever if: ESRD/ESLD, extremes of age, protein calorie malnutrition, immunosupp., steroid use.
- **Exposures**: travel, occupation/hobbies, animals, sexual contacts, TB. Consider geography, season, and incubation time in relation to exposures.
- **Physical exam**: look for thrush, dental caries; full eye exam; cardiac murmurs; HSM; abd tenderness; rash/skin lesions; LAN; synovitis; complete neuro exam

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Fever of Unknown Origin (FUO)

Definition & etiologies (*NEJM* 2022;386:463)

- **Fever** (as per above def) on >1 occasion during ≥3 wk & **no dx** despite 1 wk of evaluation
- More likely to be *unusual manifestation of common disease* than an uncommon disease

- In Pts with HIV: >75% causes are infectious, but *rarely due to HIV itself*
- *Frequent reassessment needed* to identify focal signs and progression of disease

Category	Etiologies of Classic FUO (*Medicine* 2007;86:26; *AJM* 2015;128:1138)
Infection ~30%	**Tuberculosis:** disseminated or extrapulm. disease can have normal CXR, PPD/IGRA, sputum AFB; bx (lung, liver, bone marrow) for granulomas has 80–90% yield in miliary disease **Endocarditis:** if blood cxs neg consider *Bartonella*, *Coxiella*, etc. Abscess: dental, paraspinal, hepatic, splenic, subphrenic, pancreatic, perinephric, pelvic, prostatic, appendiceal Osteomyelitis, sinusitis, typhoid, 1° CMV or EBV, malaria, *Babesia*
Connective tissue disease ~30%	**Giant cell arteritis/**PMR**:** headache, scalp pain, jaw claudication, visual disturbances, myalgias, arthralgias, ↑ ESR **Adult-onset Still's:** evanescent truncal rash, LAN, pharyngitis, ↑↑ ferritin PAN, ANCA ⊕, other vascul.; SLE, RA, psoriatic or reactive arthritis
Neoplasm ~20%	**Lymphoma:** LAN, HSM, ↓ Hct or plt, ↑ LDH; leukemia; myelodysplasia **Renal cell carcinoma:** microscopic hematuria, ↑ Hct HCC, pancreatic and colon cancers, sarcomas, mastocytosis Atrial myxomas: obstruction, embolism, constitutional symptoms
Misc ~20%	**Drug fever**, factitious, DVT/PE, hematoma Thyroiditis or thyroid storm, adrenal insufficiency, pheochromocytoma Granulomatous hepatitis (many causes), **sarcoidosis**, Kikuchi's, Behçet's Familial Mediterranean fever (peritonitis, episodic fever, pleuritis; ↑ WBC & ESR during attacks); other defects in innate immunity

More common causes boldfaced

Workup (*Archives* 2009;169:2018; *AJM* 2015;128:1138)

- Initial: CBC w/ diff, CMP, ESR, CRP, 3 sets BCx (off abx), U/A, UCx, CXR
- Additional workup based on sx: ANA, RF, cryoglobulin, LDH, CK/aldolase, SPEP, TFTs, PPD or IGRA, HIV Ag/Ab ± PCR, RPR, EBV serologies, CMV PCR, HBV/HCV serologies
- Consider imaging: chest & abd CT, FDG-PET (*Am J Med* 2024;137:629), TTE, LE duplex US
- Tissue dx: consider bx of LN (excisional preferred), liver (especially if ↑ Aϕ), temporal artery (for GCA), BM, kidney (RPGN)

Treatment

- Empiric abx *not* indicated (unless Pt neutropenic or critically ill)
- Empiric glucocorticoids not indicated unless strong suspicion for specific rheumatologic dx
- Stop unnecessary meds (only 20% with a med cause have eos or rash)
- Up to 30% of cases remain undiagnosed, most spontaneously defervesce (wks to mos)

Fever and Rash

Approach to diagnostic workup

- *Meningococcemia, endocarditis, RMSF, sepsis, & toxic shock need urgent dx & Rx*
- Workup: CBC w/diff, BMP, LFTs, LDH, CK, U/A, HIV Ag/Ab ± PCR, BCx (off abx)
- To narrow Ddx: characterize time course of rash, progression, & morphology
- **Erythema multiforme**: symmetric "target" lesions often of palms, soles, & mucous memb
  Infxn etiol: HSV, *Mycoplasma*, syphilis, VZV, EBV, CMV, adenovirus, etc.
  Non-infxn etiol: most likely meds (eg, NSAIDs, sulfa, AEDs), autoimmune disease
- **Erythema nodosum**: tender erythematous or violaceous nodules usually symmetric on LE

Infxn etiol: Strep, TB, EBV, *Bartonella*, HBV, psittacosis, fungal, *L. venereum*, etc.
Non-infxn etiol: sarcoidosis, IBD, Behçet's, other rheum, pregnancy/OCP use

- Pursue specific dx based on exposure hx & exam, including serologies, viral PCRs, possibly skin biopsy ± exam of vesicular or bullae fluid if present
- Immunosupp. Pts need broad w/u; higher risk of disseminated/rapidly progressive infxns

Exposure or Risk Factor	Possible Infectious Etiology
Summer/fall > other seasons	Enterovirus
Winter	Parvovirus, Meningococcemia
Spring/summer	Lyme, RMSF, Ehrlichiosis, Anaplasmosis
Year-round	Adenovirus, *Mycoplasma*
Mammal exposure	*Bartonella* (cat), *Pasteurella* (cat > dog), *Toxoplasma* (cat), *Capnocytophaga* (cat/dog), rat bite fever
Arachnid bite	Lyme (tick), RMSF (tick), *Ehrlichia* (tick), *Anaplasma* (tick), rickettsialpox (mite), scrub typhus (chigger)
Adult <30 y	Mononucleosis (EBV or CMV)
Inadequate immunization	Measles, Rubella, VZV, influenza
Sexually active	HIV, syphilis, disseminated gonococcus, HSV, mpox
Consider noninfectious causes: allergy/DRESS, DVT, phlebitis, vasculitides, neutrophilic dermatoses, gout, connective tissues dis., malignancy, foreign body rxn	

Treatment

- Empiric abx *not* indicated (unless Pt neutropenic or critically ill)
- Consider important empiric isolation precautions (eg, varicella → airborne/contact; measles → airborne; meningococcus → droplet) while workup pending

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Fever in a Returned Traveler

See CDC.gov/travel for up-to-date information on regional risks and recommendations

Region or Exposure	Common Etiologies (*NEJM* 2017;376:548)
Sub-Saharan Africa	**Malaria** >> dengue and other arboviruses, rickettsial disease, enteric fever
South/Southeast Asia	Dengue > malaria, enteric fever (*S. typhi/paratyphi*), Chikungunya and other arboviruses, rickettsial disease
Central & S. America	Dengue, enteric fever, malaria
Caribbean & Mexico	Dengue >> Chikungunya and other arboviruses > enteric fever, malaria
Middle East	Middle East Respiratory Syndrome, brucellosis
Freshwater	Schistosomiasis, leptospirosis

swimming	
Unpurified drinking water	Enteric disease (*E. coli* >> *S. typhi*, *Campylobacter*, hepatitis E > *Vibrio cholerae*), amoebic liver abscess
Inadequate immunization	HAV/HBV, *S. typhi*, influenza, measles, rubella, yellow fever

- Pts visiting friends and relatives abroad are most likely to contract illness during travel
- Also consider domestic infxns, influenza/COVID-19, STIs, & non-infxn causes

Select clinical manifestations

- **Ebola:** fever in traveler from area with active transmission of Ebola w/in 21 d
- **Malaria** (*NEJM* 2025;392:1320): nonspecific sx incl. diarrhea, H/A, myalgias, cough, ΔMS
- **Dengue:** nonspecific sx including headache, severe myalgias, rash/petechiae
- **Chikungunya:** nonspecific sx including joint pain, moderate myalgias
- **Typhoid** (*Lancet* 2015;385:1136): diarrhea/constipation, abd pain, ± rash, relative bradycardia
- **Rickettsial disease:** headache, myalgias, lymphadenopathy, ± rash/eschar
- **Zika:** rash, arthralgia, headache, conjunctivitis; often less severe than dengue, Chikungunya

Workup

- Routine testing: CBC w/ diff, BMP, LFTs, BCx, UA, rapid malaria test
- **Fever in a traveler from a malaria zone is malaria until proven otherwise; consider a medical emergency → hospitalization & empiric Rx.** One ⊖ smear does *not* r/o.
- Other tests based on s/s, labs, exposure, incubation period, geography, and seasonality. O&P exam, CXR, blood smears for filaria/Babesiosis/*Borrelia*, serologies, STI & HIV, PPD or IGRA, bone marrow aspirate, bx of lymph nodes or skin lesions, CSF studies.

PITUITARY DISORDERS

HYPOPITUITARY SYNDROMES (*Lancet* 2016;388:2403; *JCEM* 2016;11:3888)

Etiologies

- **Primary:** surgery, XRT (develops after ~4–5 y), tumors (primary or metastatic), infection, infiltration (sarcoid, hemochromatosis), autoimmune, ischemia (including Sheehan's syndrome caused by pituitary infarction intrapartum), carotid aneurysms, cavernous sinus thrombosis, trauma, meds (eg, CTLA4/PD-L1/PD-1 inhib), apoplexy, empty sella, genetic
- **Secondary:** (hypothalamic dysfunction or stalk interruption): tumors (including craniopharyngioma), infection, infiltration, radiation, surgery, trauma

Clinical manifestations

- **Hormonal deficiencies:** ACTH, TSH, FSH and LH, GH, prolactin, and ADH
- **Panhypopituitarism:** deficiencies in multiple hormonal axes
- **Mass effect:** headache, visual field Δs, cranial nerve palsies

Central adrenal insufficiency: ↓ ACTH

- Sx similar to primary adrenal insufficiency (see "Adrenal Disorders") *except:*
  no salt cravings or hyperkalemia (b/c aldo preserved)
  no hyperpigmentation (b/c ACTH/MSH is not ↑)

Central hypothyroidism: ↓ TSH

- Sx of central hypothyroidism similar to 1° (see "Thyroid Disorders") *except* absence of goiter
- Dx w/ free T_4 (low) and TSH (may be low or *inappropriately nl*). Trend only free T4 after dx.

Hypoprolactinemia: ↓ prolactin

- Most common cause is Sheehan's syndrome (*Gynec Endo* 2013;29:292)
- Consider in postpartum women unable to lactate or with failure of menstrual resumption

Growth hormone deficiency: ↓ GH

- ↑ chronic risk for osteoporosis, fatigue, decreased lean body mass
- Dx: failure to ↑ GH w/ approp. stimulus (eg, insulin tolerance test, glucagon or macimorelin)
- GH replacement in adults controversial (*Annals* 2003;35:419; *NEJM* 2019;380:2551)

Central hypogonadism: ↓ FSH & LH

- Clinical manifestations: ↓ libido, impotence, oligomenorrhea or amenorrhea, infertility, ↓ muscle mass, osteoporosis
- Physical exam: ↓ testicular size; loss of axillary, pubic, and body hair
- Dx with: ↓ a.m. testosterone or estradiol (also assess SHBG, esp. in obese) and ↓ or normal FSH/LH (all levels ↓ in acute illness, ∴ do not measure in hospitalized Pts)
- Treatment: testosterone or estrogen replacement vs. correction of the underlying cause

Central diabetes insipidus: ↓ ADH

- Typically 2/2 mass lesion *extrinsic* to sella; pit. tumors do not typically present w/ AVP defic.
- Clinical manifestations: *severe* polyuria, thirst, nl to *mild* hyperNa (*severe* if ↓ access to H_2O)
- Diagnostic studies & Rx: see "Sodium and Water Homeostasis" in Nephrology section

Pituitary apoplexy (*Endocr Rev* 2015;36:622)

- Rapid expansion of pituitary tumor (typically adenoma) due to hemorrhage or infarction
- Sx include excruciating headache, diplopia, hypopituitarism
- Rx: immediate high-dose glucocorticoids; prompt surgical decompression if severe neurologic impairment or Δ MS; conservative management if mild

Diagnostic evaluation

- **Hormonal studies**
  Chronic: ↓ target gland hormone + ↓ or (inappropriately) normal trophic pituitary hormone
  Acute: will develop ↓ target gland hormone; nb, in central adrenal insufficiency cortisol deficiency develops, but ACTH stim may be nl since adrenal atrophy takes 4–6 weeks
  Partial hypopituitarism is more common than panhypopituitarism
- **Pituitary MRI:** pituitary protocol (contrast enhanced) recommended

Treatment

- **Replace deficient target gland hormones**
- Most important deficiencies to recognize and treat in inpatients are *adrenal insufficiency* and *hypothyroidism*; if both present, treat with glucocorticoids first, then replace thyroid hormone so as not to precipitate adrenal crisis

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Hyperpituitary Syndromes

Pituitary tumors (*NEJM* 2020;382:937; *JAMA* 2023;329:1386)

- **Pathophysiology: adenoma** → excess of trophic hormone (if tumor fxnal, but 30–40% not) and potentially *deficiencies* in other trophic hormones due to compression
- Clinical manifestations: specific syndromes due to oversecretion of hormones (vide infra) ± nonspecific mass effect: headache, visual Δs, diplopia, cranial neuropathies
- Workup: MRI brain pituitary protocol, hormone levels, ± visual field testing
  if <10 mm, no mass effect, no hormone overproduction, can f/up in 12 mos

Hyperprolactinemia (*JCEM* 2023;108:2400)

- Etiology
  Prolactinoma (50% of pituitary adenomas); typically PRL is >100
  Stalk compression due to mass → ↓ inhibitory dopamine → ↑ PRL (mild, usually <100)
- Physiology: PRL induces lactation and inhibits GnRH → ↓ FSH & LH; co-secretion of PRL and growth hormone in 10% of prolactinomas
- Clinical manifestations: **amenorrhea**, **galactorrhea**, **infertility**, ↓ libido, impotence
- Diagnostic studies
  ↑ **PRL** (✓ *fasting* levels), but ↑ in many situations, ∴ r/o preg. or exogenous estrogens, hypothyroidism, dopamine agonists (eg, psych meds, antiemetics), renal failure (↓ clearance), cirrhosis, stress, ↑ carb diet, vigorous exercise. Watch for *hook effect*: assay artefact yields falsely low PRL if very high (>1000) serum PRL; retest with diluted sample.
  MRI brain pituitary protocol
- Treatment
  If **asx** (no HA, galactorrhea, hypogonadal sx) & microadenoma (<**10 mm**), follow w/ MRI
  If **sx** or macroadenoma (≥**10 mm**) options include:

Medical w/ dopa agonist such as cabergoline (70–100% success rate) or bromocriptine (not as well tol); side effects include N/V, orthostasis, mental fogginess, exacerbation of psych illness. Intravaginal bromocriptine: ↓ GI side effects. Fertility likely ↑ w/ med Rx; once pregnant stop medical mgmt. except if macroadenomas or aggressive disease.

Surgical: transsphenoidal surgery (main indications: failed or cannot tolerate medical Rx, GH cosecretion or neurologic sx not improving); 10–20% recurrence rate

Radiation: if medical or surgical therapy has failed or is not tolerated

Acromegaly (↑ GH; **1**0% of adenomas; *Nat Rev Dis Primer* 2019;5:1)

- Physiology: stimulates secretion of insulin-like growth factor 1 (IGF-1)
- Clinical manifestations: ↑ soft tissue, arthralgias, jaw enlargement, headache, carpal tunnel syndrome, macroglossia, hoarseness, sleep apnea, amenorrhea, impotence, diabetes mellitus, acanthosis/skin tags, ↑ sweating, HTN/CMP, colonic polyps, neuropathies
- Diagnostic studies: *low utility in checking random GH levels because of pulsatile secretion*
  ↑ **IGF-1** (somatomedin C); ± ↑ PRL; OGTT → GH *not* suppressed to <1 (<0.3 if newer assay) ng/mL; pituitary MRI to evaluate for tumor
- Treatment: **surgery**, octreotide (long- and short-acting preparations), dopamine agonists (if PRL cosecretion), pegvisomant (GH receptor antagonist), radiation
- Prognosis: w/ and w/o Rx ↑ mortality, risk of pituitary insufficiency, colon cancer

Central hyperthyroidism (↑ TSH, ↑ α-subunit): extremely rare; see “Thyroid Disorders”

↑ **FSH & LH:** often non-fxnal, may present as *hypopituitarism* b/c of compression effects

Multiple Endocrine Neoplasia (MEN) Syndromes	
Type	**Main Features**
1 (*MENIN* inactiv.)	Parathyroid hyperplasia/adenomas → ↑ Ca (~100% penetrance) Pancreatic islet cell neoplasia (gastrin, VIP, insulin, glucagon) Pituitary adenomas (fxn or non-fxn) and other tumors
2A (*RET* proto-oncogene)	Medullary thyroid carcinoma (MTC) (~99%) Pheo (~50%) Parathyroid hyperplasia → hypercalcemia (15–20%)
2B (*RET* proto-oncogene)	Medullary thyroid carcinoma (~99%) Pheo (~50%) Mucosal and gastrointestinal neuromas, marfanoid habitus
4 (*CDKN1B*)	Parathyroid hyperplasia/adenomas (~90%) Pituitary adenomas (fxnal or non-fxnal) Gastroenteropancreatic neuroendocrine tumors (~25%) Adrenal, kidney, reproductive organ tumors

Autoimmune Polyglandular Syndromes (APS) (*NEJM* 2018;378:1132)	
Type	**Features**
I (APECED)	Childhood onset, mucocutaneous candidiasis, hypoparathyroidism, adrenal insufficiency, monogenetic: biallelic AIRE mutation
II	Adult onset, adrenal insufficiency, autoimmune thyroid disease, diabetes mellitus type 1; polygenic

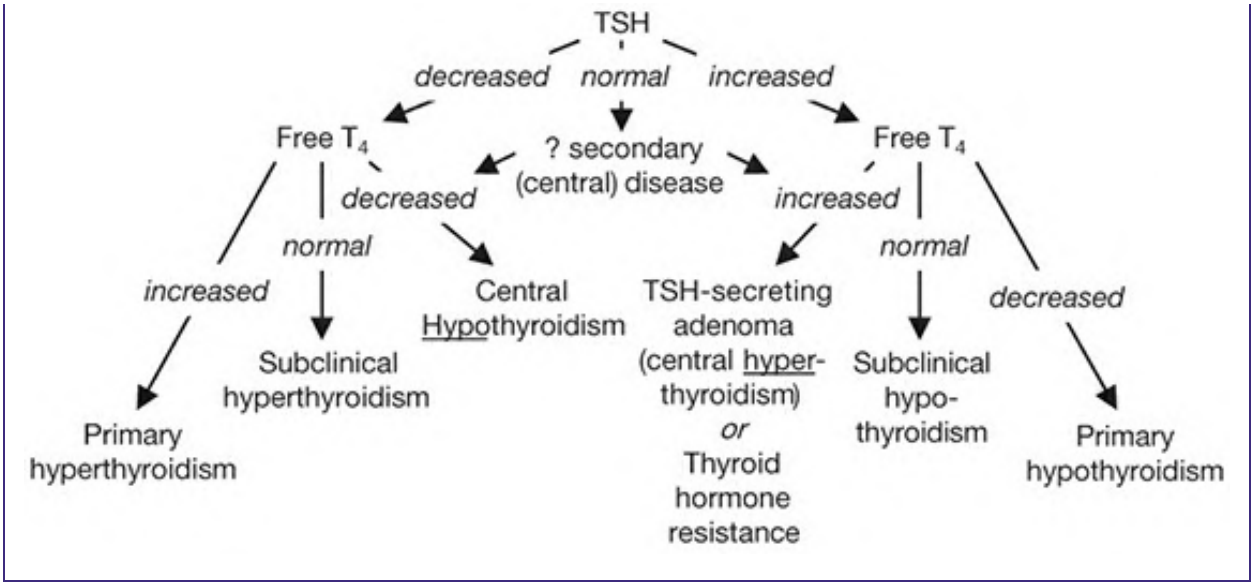
THYROID DISORDERS

Common Diagnostic Tests in Thyroid Disorders	
Test	**Comments**
Thyroid-stimulating hormone (TSH)	*Most sensitive test* to detect 1° hypo- and hyperthyroidism. **Used as primary screening test for thyroid disease.** ↓'d by dopa, glucocorticoids, severe illness, excessive biotin. May not be helpful in central hypothyroidism.
Free T_4 (fT_4)	Unbound T_4, not influenced by TBG. Heparin and furosemide can affect TBG–FT4 binding and lead to falsely high FT4 on assay.
Total T_3	*Total* serum concentrations of T_3 (liothyronine). Useful when evaluating for *hyperthyroidism*.
Antithyroid peroxidase Ab (anti-TPO)	Antithyroid peroxidase (TPO) seen in Hashimoto's (high titer), painless subacute thyroiditis, and Graves' disease (low titer)

(*Lancet* 2001;357:619 & *Thyroid* 2003;13:19)

Specialized Diagnostic Tests in Thyroid Disorders	
Test	**Comments**
Total T_4	*Total* serum concentrations ($\therefore$ influenced by TBG). Checked if concern that TSH and free T_4 are not accurate.
Free T_3	Unbound T_3, low clinical utility
Reverse T_3	Inactive, ↑'d in sick euthyroid syndrome. Rarely used clinically.
Thyroid-stimulating Abs	Thyroid-stimulating Ig (TSI, functional assay, reflecting stimulation) & thyrotropin-binding inhibitory immunoglobulin (TBII, binding assay, reflecting affinity and specificity); seen in Graves' disease
Thyroglobulin	↑'d in goiter, hyperthyroidism, and thyroiditis ↓'d in factitious ingestion of thyroid hormone Tumor marker for thyroid cancer only after total thyroidectomy and radioiodine therapy
Thyroxine-binding globulin (TBG)	↑ TBG ($\therefore$ ↑ T_4): estrogen (OCP, preg.), hepatitis, opioids, hereditary ↓ TBG ($\therefore$ ↓ T_4): androgens, glucocorticoids, nephrotic syndrome, cirrhosis, acromegaly, antiepileptics, hereditary
Radioactive iodine uptake (RAIU) scan	Useful to differentiate causes of hyperthyroidism. TSH must be suppressed at time of scan for interpretation of pathologic cause. ↑ **uptake:** Graves' disease, toxic multinodular goiter or hot nodule **no uptake:** subacute painful (de Quervain's) or silent thyroiditis, exog. thyroid hormone, recent I load, struma ovarii, or antithyroid Rx

Figure 7-1 Approach to TSH levels



HYPOTHYROIDISM (*Lancet* 2024;404:1347)

Etiologies

- Primary (>90% of cases of hypothyroidism; ↓ **free T_4,** ↑ TSH)
  - Goitrous: **Hashimoto's thyroiditis** (after hyperthyroid phase of thyroiditis), iodine deficiency, lithium, amiodarone, PD-1/CTLA4i-mediated burnout (hyper → hypothyroid)
  - Non-goitrous: surgical destruction, s/p radioactive iodine or XRT, amiodarone
- Secondary (central): ↓ free T_4; TSH low, inappropriately nl, or slightly high (although functionally inactive due to abnormal glycosylation); due to hypothalamic or pituitary failure

Hashimoto's thyroiditis

- Autoimmune destruction w/ lymphocytic infiltration, can see in APS Type II (qv)
- ⊕ antithyroid peroxidase (anti-TPO) and antithyroglobulin (anti-Tg) Abs in >90%

Clinical manifestations (*Annals* 2020;173:ITC1)

- **Early:** weakness, fatigue, arthralgias, myalgias, headache, depression, cold intolerance, weight gain, constipation, menorrhagia, dry skin, coarse brittle hair, brittle nails, carpal tunnel syndrome, delayed DTRs ("hung up" reflexes), diastolic HTN, hyperlipidemia
- **Late:** slow speech; hoarseness; loss of outer third of eyebrows; **myxedema** (nonpitting skin thickening due to ↑ glycosaminoglycans); periorbital puffiness; bradycardia; pleural, pericardial, & peritoneal effusions; atherosclerosis
- **Myxedema crisis:** vide infra

Diagnostic studies (*Lancet* 2017;390:1550)

- ↓ **free T_4;** ↑ **TSH** in 1º hypothyroidism; ⊕ antithyroid Ab (TPO) in Hashimoto's thyroiditis
- May see hypoNa, hypoglycemia, anemia, ↑ LDL, ↓ HDL, ↑ CK, macrocytic anemia
- Screening recommended for pregnant women

Treatment of overt hypothyroidism (*Endocrine* 2019;66:18)

- Levothyroxine (1.5–1.7 µg/kg/d), re ✓ TSH q4–6wk, titrate q8–12wks if TSH not in range

- *Lower starting dose* (0.3–0.5 µg/kg/d) if at risk for ischemic heart disease or elderly
- ↑ dose typically needed if:
  - poor GI absorption: meds that ↓ absorption (iron, calcium, cholestyramine, sucralfate, PPI), celiac disease, IBD
  - meds that accelerate T_4 catabolism (eg, phenytoin, phenobarbital, rifampin)
  - initiation of estrogen replacement; pregnancy (~30% ↑ by wk 8): TSH goals change by trimester: 1st = 0.1–4.0 mIU/L, 2nd & 3rd = gradual return of TSH to nonpregnant nl range (*Thyroid* 2017;3:315)

Subclinical hypothyroidism (*NEJM* 2017;376:2556; *JAMA* 2019;322:153)

- Mild ↑ TSH and **normal free T_4** with only subtle or no sx
- If TSH <7 or ⊖ anti-TPO Ab, ~½ resolve after 2 y (*JCEM* 2012;97:1962)
  - if ↑ titers of antithyroid Abs, progression to overt hypothyroidism is ~4%/y
- No clear benefit to Rx (*NEJM* 2017;376:2534). In practice, follow expectantly or Rx to improve mild sx or dyslipidemia. Experts often Rx if TSH >10 mU/L, goiter, pregnancy, or infertility.

Myxedema coma (ie, profound hypothyroidism; *Thyroid* 2014;24:1670)

- Presentation: hypothermia, hypotension, hypoventilation, Δ MS (coma rare), hyponatremia, hypoglycemia; often precipitated by infxn or major cardiopulmonary or neurologic illness
- Treatment: supportive care most important. Slow metabolism of drugs can lead to coma. Correction of hypothyroidism takes time. Load 200–400 µg T_4 IV, then 50–100 µg IV qd; b/c peripheral conversion impaired, in rare cases, may also give 5–20 µg T_3 IV q8h if unstable w/ bradycardia and/or hypothermia (T_3 more arrhythmogenic); must give **empiric *glucocorticoid replacement Rx*** first as ↓ adrenal reserves in myxedema coma.

Hyperthyroidism (*JAMA* 2023;330:1472; *Lancet* 2024;403:768)

Etiologies

- **Graves' disease** (60–80% of thyrotoxicosis)
- **Thyroiditis:** thyrotoxic phase of subacute (granulomatous) or painless (lymphocytic)
- **Toxic adenomas** (single or multinodular goiter)
- Extremely rare: TSH-secreting pituitary tumor or pituitary resistant to thyroid hormone (↑ TSH, ↑ free T_4)
- Misc: amiodarone, iodine-induced, thyrotoxicosis factitia, struma ovarii (3% of ovarian dermoid tumors and teratomas), tumors (eg, choriocarcinoma) secreting hCG (weak bioactivity against TSH-R), large deposits of metastatic follicular thyroid cancer

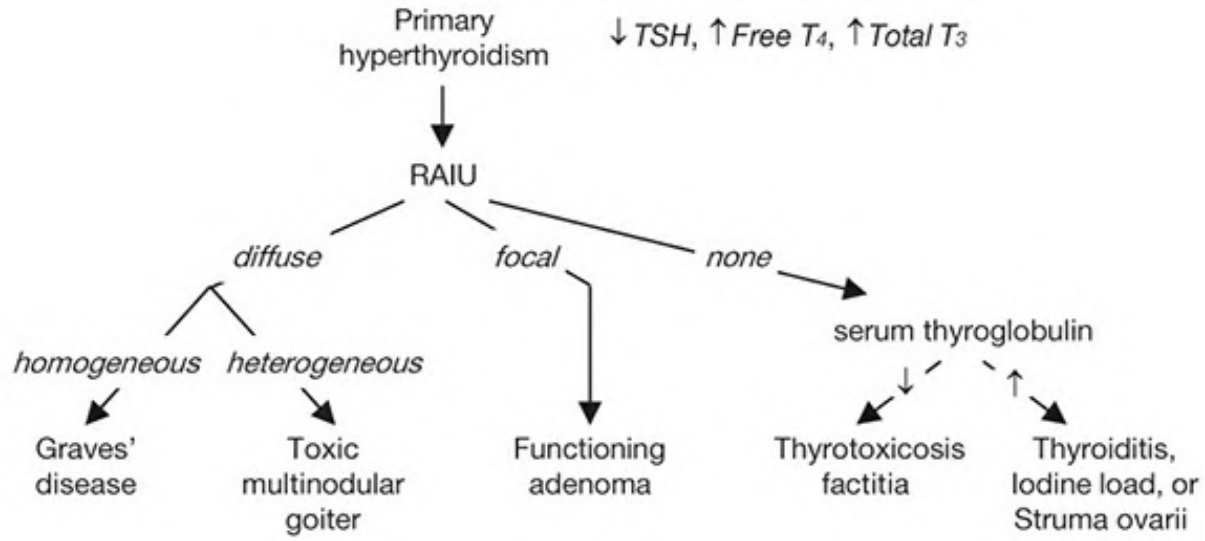
Clinical manifestations

- Restlessness, tremor, moist, warm skin, fine hair, ↑ HR, AF, weight loss, ↑ frequency of stools, menstrual irregularities, hyperreflexia, osteoporosis, stare, and lid lag (2/2 sympathetic overactivity)
- **Apathetic thyrotoxicosis:** seen in elderly who can present with lethargy as only sx

Laboratory testing

- ↑ **free T_4** and **total T_3;** ↓ **TSH** (except in TSH-secreting tumors)
- **RAIU scan** is very useful study to differentiate causes (see table on page 7-3); cannot do if recent IV contrast or amio load b/c iodine blocks uptake, so ✓ autoantibodies instead
- Rarely need to ✓ for autoantibodies except in pregnancy (to assess risk of fetal Graves')
- May see hypercalciuria ± hypercalcemia, ↑ Aϕ, anemia

Figure 7-2 Workup of primary hyperthyroidism



Graves' disease (*NEJM* 2016;375:1552)

- ♀:♂ ratio is 5–10:1, most Pts between 40 and 60 y at dx
- Dx: ⊕ **thyroid antibodies:** TSI or TBII (⊕ in 80%), anti-TPO, antithyroglobulin; ANA; hypervascular thyroid on Doppler U/S, T3/T4 ratio usually >20
- Clinical manifestations in addition to those of hyperthyroidism (vide supra):
  - **Goiter:** diffuse, nontender, w/ thyroid bruit
  - **Ophthalmopathy** (*NEJM* 2010;362:726): seen in 50%; up to 90% if formally tested. Periorbital edema, lid retraction, proptosis, conjunctivitis, diplopia (EOM infiltration); associated w/ smoking. Stare and lid lag seen in any type of hyperthyroidism.
  - **Pretibial myxedema (3%):** infiltrative dermopathy

Thyroiditis (*NEJM* 2003;348:2646; *Med Clin North Am* 2012;96:223)

- **Acute:** bacterial infection (very rare in U.S. except postsurgical), typically *Staph/Strep* spp.
- **Subacute:** transient thyrotoxicosis → transient hypothyroidism → normal thyroid fxn
  - **Painful** (viral, granulomatous or de Quervain's): fever, ↑ ESR; Rx = NSAIDs, ASA, steroids
  - **Silent** (postpartum, autoimmune including Hashimoto's, or lymphocytic): painless, ⊕ TPO Abs; if postpartum, can recur with subsequent pregnancies
  - **Other:** meds (amio, lithium, TKIs, PD-L1/CTLA4i), palpation thyroiditis, postradiation

Treatment (*Thyroid* 2016;26:1343; *JCEM* 2020;105:3704)

- β-blockers: control tachycardia (propranolol also ↓ T_4 → T_3 conversion)
- Graves' disease: either antithyroid drugs or radioactive iodine (*NEJM* 2016;375:1552)
  - **methimazole:** 60% chance of recurrence after 1 y; side effects include pruritus, rash, arthralgia, fever, N/V, and *agranulocytosis* in 0.5%. PTU: 2nd line (risk of hepatocellular necrosis; TID dosing; slower effect; *JCEM* 2007;92:2157). For both, need to ✓ LFTs, WBC, TSH at baseline and in follow-up.
  - **radioactive iodine (RAI)** (*NEJM* 2011;364:542): typically done as outPt; preRx w/ antithyroid drugs in selected Pts w/ CV disease or elderly to prevent ↑ thyrotoxicosis, stop 3 d before to allow RAI uptake; >75% of treated Pts become hypothyroid
  - **surgery:** less commonly chosen for Graves', usually for Pts w/ obstructive goiter or ophthalmopathy. Adverse effects hypoparathyroidism, recurrent laryngeal nerve injury.

- Ophthalmopathy: can worsen after RAI; prophylax w/ prednisone in high-risk Pts; can be Rx'd w/ selenium, glucocorticoids, teprotumumab (IGF-1R inhibitor), radiation, and/or surgical decompression of orbits (*NEJM* 2009;360:994)
- Toxic adenoma or toxic multinodular goiter: RAI, radiofrequency ablation, or surgery (methimazole preRx for surgery, in selected patients before RAI)

Subclinical hyperthyroidism (*NEJM* 2018;378:2411)

- Mild ↓ TSH and **normal free T_4** with only subtle or no sx
- ~15% → overt hyperthyroidism in 2 y; ↑ risk of AF, CHD, fracture (*JAMA* 2015;313:2055)
- Rx controversial: consider if TSH <0.1 mU/L and ↑ risk for CV disease or osteopenic

Thyroid storm (extremely rare; *JCEM* 2015;2:451)

- Dx: no universal criteria. Pt presents w/ s/s thyrotoxicosis (possibly including systolic HTN, wide pulse pressure, tachycardia, fever, delirium). Burch–Wartofsky scale (*Endocrinol Metab Clin North Am* 1993;22:263) can assess likelihood that s/s = thyroid storm. 20–30% mortality, but very rare so consider additional dx.
- Tx: β-blocker (always assess for h/o CHF prior to Rx), PTU or methimazole, iopanoic acid or iodide (for Wolff–Chaikoff effect) >1 h after PTU, ± steroids (↓ T_4 → T_3)

Nonthyroidal Illness (Sick Euthyroid Syndrome) (*Lancet D&E* 2015;3:816)

- TFT abnormalities in Pts w/ severe nonthyroidal illness (∴ in acute illness, ✓ TFTs only if ↑ concern for thyroid disease); *may* have acquired transient central hypothyroidism
- If thyroid dysfxn suspected in critically ill Pt, TSH alone not reliable; must measure total T_4, free T_4, & T_3
- Mild illness: ↓T_4 → T_3 conversion, ↑ rT_3 → ↓ T_3; in severe illness: ↓ TBG & albumin, ↑↑ rT_3 → ↓↓ T_3, ↑ degradation of T_4, central ↓ TSH → ↓↓ **T_3**, ↓↓ **T_4**, ↓ free **T_4**, ↓ **TSH**
- Recovery phase: ↑ TSH followed by recovery of T_4 and then T_3 (typically 2–4 wks)
- Replacement Rx not helpful for critically ill Pts w/ ↓ T_3 & T_4 unless s/s of hypothyroidism

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Amiodarone and Thyroid Disease

Overview (*JCEM* 2021;106:226)

- 6 mg iodine per 200-mg tablet, risk of thyroid dysfunction lower w/ lower amio doses
- ✓ TSH prior to therapy, then after amio started at 4-mo intervals and for 1 y after amio d/c'd (thyroid disease can occur at any point from time amio given to 18 mos later)

Hypothyroidism (occurs in ~10%; more common in iodine-replete areas)

- Pathophysiology
  1. Wolff–Chaikoff effect: iodine load ↓ I^- uptake, organification and release of T_4 & T_3
  2. inhibits T_4 → T_3 conversion
  3. ? direct/immune-mediated thyroid destruction
- Normal individuals: ↓ T_4; then escape Wolff–Chaikoff effect and have ↑ T_4, ↓ T_3, ↑ TSH; then TSH normalizes (after 1–3 mo)
- Susceptible individuals (eg, subclinical Hashimoto's, ∴ ✓ anti-TPO) do *not* escape effects
- Treatment: thyroxine to normalize TSH; may need larger than usual dose

Hyperthyroidism (3% of Pts on amio; ~10–20% of Pts ***in iodine-deficient areas***)

- Type 1 = underlying multinodular goiter or autonomous thyroid tissue

Jod–Basedow effect: iodine load → ↑ **synthesis** of T_4 and T_3 in autonomous tissue

- Type 2 = destructive thyroiditis
  ↑ **release** of preformed T_4 & T_3 → hyperthyroidism → hypothyroidism → recovery
- Doppler U/S: type 1 w/ ↑ thyroid blood flow; type 2 w/ ↓ flow
- Treatment: not absolutely necessary to d/c amio b/c amio ↓ T_4 → T_3 conversion methimazole for type 1; steroids (eg, 40 mg prednisone qd) for type 2 often difficult to distinguish, so Rx for both typically initiated (*JCEM* 2001;86:3)
  consider thyroidectomy in severely ill patient

Thyroid Cancer (*Thyroid* 2016;26:1; *Endo Metab Clin NA* 2019;48:23)

Thyroid nodules (*JAMA* 2018;319:914)

- Prevalence 5–10% (50–60% if screen with U/S), ♀ > ♂, ~7–15% malignant
- Screening U/S recommended if FHx of MEN2 or medullary thyroid cancer, personal h/o neck XRT, palpable nodules or multinodular goiter
- Features a/w ↑ risk of malig: age <30 y, h/o neck XRT, family history of thyroid cancer
- U/S features a/w benign dx: cystic nodules, “spongiform” sonographic pattern
- Worrisome findings: hypoechoic, solid, irregular borders, microCa^{2+}, height>width, >20 mm
- Indications for FNA: >10-mm nodule w/ suspicious features

Papillary thyroid cancer

- Most common (85% of differentiated thyroid cancers); peak incidence 30–50 y
- Risk factors: childhood radiation exposure, FHx
- Low-risk, w/ mort. 1–2% at 20 y; mets to neck LN common, but prognosis remains good
- Rx is surgery; after surgical resection, RAI in select intermediate-risk or high-risk

Follicular thyroid cancer

- Peak incidence 40–60 y, ♀:♂ 3:1; RFs: childhood radiation; FHx
- Mortality 10–20% at 20 y; mets frequently distal due to hematogenous spread
- Hurthle cell carcinoma: pathologic dx; variant a/w poorer prognosis and ↑ recurrence rate

Anaplastic thyroid cancer (*Endo Metab Clin NA* 2019;48:269)

- ♀:♂ 1.5–2:1; poorly differentiated, extremely aggressive, mortality 90% at 5 y
- P/w rapidly growing fixed & hard neck mass, regional or distant spread in 90% at dx
- Rx options include surgery, radiation, trach, chemo, investigational clinical trials

Medullary thyroid cancer (*Endo Metab Clin NA* 2019;48:285)

- Neuroendocrine tumor of C cells, peak incidence 40–60 y, a/w MEN2A and MEN2B
- Most commonly solitary nodule; calcitonin production (presents with diarrhea, flushing) and level used to trend dz progression, dx w/ FNA (Se 50–80%); mortality 25–50% at 5 y
- Surgery first-line treatment

ADRENAL DISORDERS

Cushing’s Syndrome (Hypercortisolism)

Cushing's syndrome = cortisol excess Cushing's disease = Cushing's syndrome 2° to pituitary ACTH hypersecretion

Etiologies of hypercortisolism (*JAMA* 2023;330:170)

- Most commonly iatrogenic exogenous glucocorticoids or other meds (eg, megestrol)
- **Cushing's disease** (60–70% of non-iatrogenic CS): ACTH-secreting pituitary adenoma (micro > macro) or hyperplasia
- **Adrenal tumor** (10–15%): adenoma or (rarely) carcinoma
- **Ectopic ACTH** (10–15%): SCLC, carcinoid, islet cell tumors, medullary thyroid ca, pheo

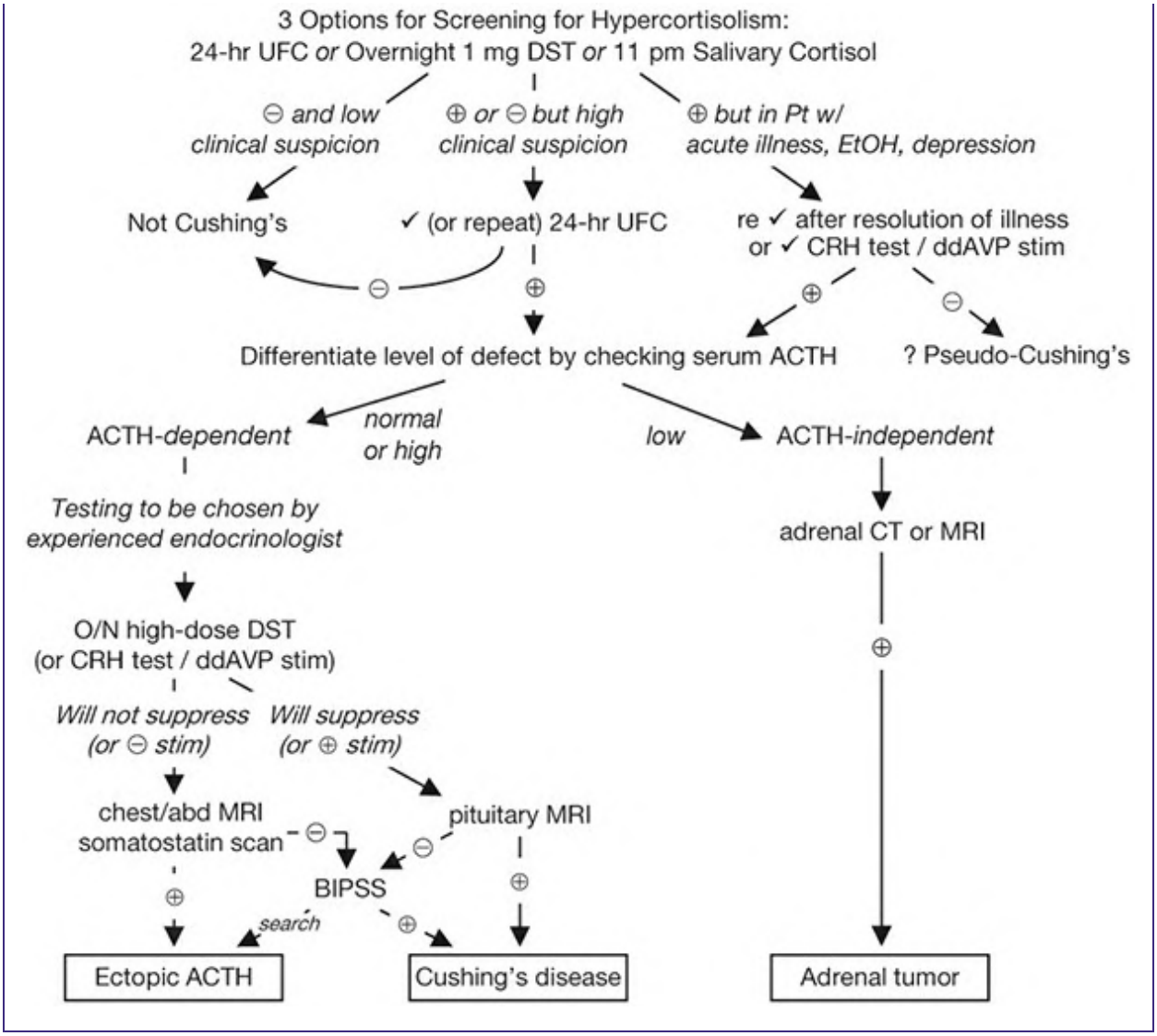
Clinical manifestations (*Lancet* 2023;402:2237)

- *Nonspecific:* glucose intolerance or DM, HTN, obesity, oligo- or amenorrhea, osteoporosis
- *More specific:* central obesity w/ extremity wasting, dorsocervical fat pads, spont. bruising
- *Most specific:* proximal myopathy, rounded facies, facial plethora, wide purple striae
- Other: depression, insomnia, psychosis, impaired cognition, hypokalemia, acne, hirsutism, hyperpigmentation (if ↑ ACTH), fungal skin infxns, nephrolithiasis, polyuria

Diagnosis

- Typically performed in outpatient setting
- *Very difficult* as inpatient b*/c hypercortisolism from acute illness and hosp.*

Figure 7-3 Approach to suspected Cushing's syndrome (*NEJM* 2017;376:1451)



CRH, corticotropin-releasing hormone; DST, dexamethasone suppression test; UFC, urinary free cortisol
Overnight 1 mg DST = give 1 mg at 11 p.m.; ✓ 8 a.m. serum cortisol (suppression if <1.8 µg/dL)
11 p.m. salivary cortisol × 2 = abnl if level ↑; 24-h UFC × 2 = abnl if level ↑, >4× ULN virtually diagnostic
O/N HD DST = 8 mg at 11 p.m.; ✓ 9 a.m. serum cortisol (suppression if <50% from day prior)
CRH stim test = 1 µg/kg IV; ✓ cortisol and ACTH (⊕ if >35% ↑ in ACTH or >20% ↑ in cortisol above baseline)
BIPSS, bilat. Inferior petrosal sinus vein sampling; ✓ central (petrosal): peripheral ACTH ratio (⊕ ≥2 basal, ≥3 after CRH), if ⊖, continue search for ectopic ACTH source and consider workup for false negative

Treatment of Cushing's syndrome (*JCEM* 2015;100:2807; *J Intern Med* 2019;286:526)

- **Surgical:** resection of pituitary adenoma, adrenal tumor or ectopic ACTH-secreting tumor, or bilateral surgical adrenalectomy if unable to control source of ACTH
- **Medical:** ketoconazole, metyrapone, osilodrostat, cabergoline, pasireotide, or mitotane to ↓ cortisol, and/or mifepristone to block cortisol action at glucocorticoid receptor; frequently used as bridge to surgery or when surgery contraindicated
- **Radiation:** can do pituitary XRT, but not effective immediately (takes 6 mo to 2 y) and is associated with risk of panhypopituitarism
- Glucocorticoid replacement × 6–36 mo after TSS (lifelong glucocorticoid + mineralocorticoid if med or surg adrenalectomy); rapid HPA axis recovery (pass ACTH stim w/in 12 mo) predictive of relapse (*JCEM* 1995;80:3114)

Etiologies

- **Primary** (adrenal disorders, renin-independent increase in aldosterone; *JCEM* 2015;100:1) adrenal hyperplasia (60–70%), adenoma (**Conn's syndrome**, 30–40%), adrenocortical cancer, glucocorticoid-remediable aldosteronism (GRA; ACTH-dep. rearranged promoter)
- **Secondary** (extra-adrenal disorders, ↑ aldosterone is renin-dependent)
  - Primary reninism: renin-secreting tumor (very rare)
  - Secondary reninism: renovascular disease: RAS, malignant hypertension; edematous states w/ ↓ effective arterial volume: CHF, cirrhosis, nephrotic syndrome; hypovolemia, diuretics, T2D, Bartter's (defective Na/K/2Cl transporter ≈ receiving loop diuretic), Gitelman's (defective renal Na/Cl transporter ≈ receiving thiazide diuretic)
- **Nonaldosterone mineralocorticoid excess** mimics hyperaldosteronism
  - 11β-HSD2 defic. (→ lack of inactivation of cortisol, which binds to mineralocorticoid recept.)
  - Black licorice (glycyrrhizic acid inhibits 11β-HSD2), extreme hypercortisolism (overwhelming 11β-HSD2), exogenous mineralocorticoids
  - Liddle's syndrome (constitutively activated/overexpressed distal tubular renal Na channel)

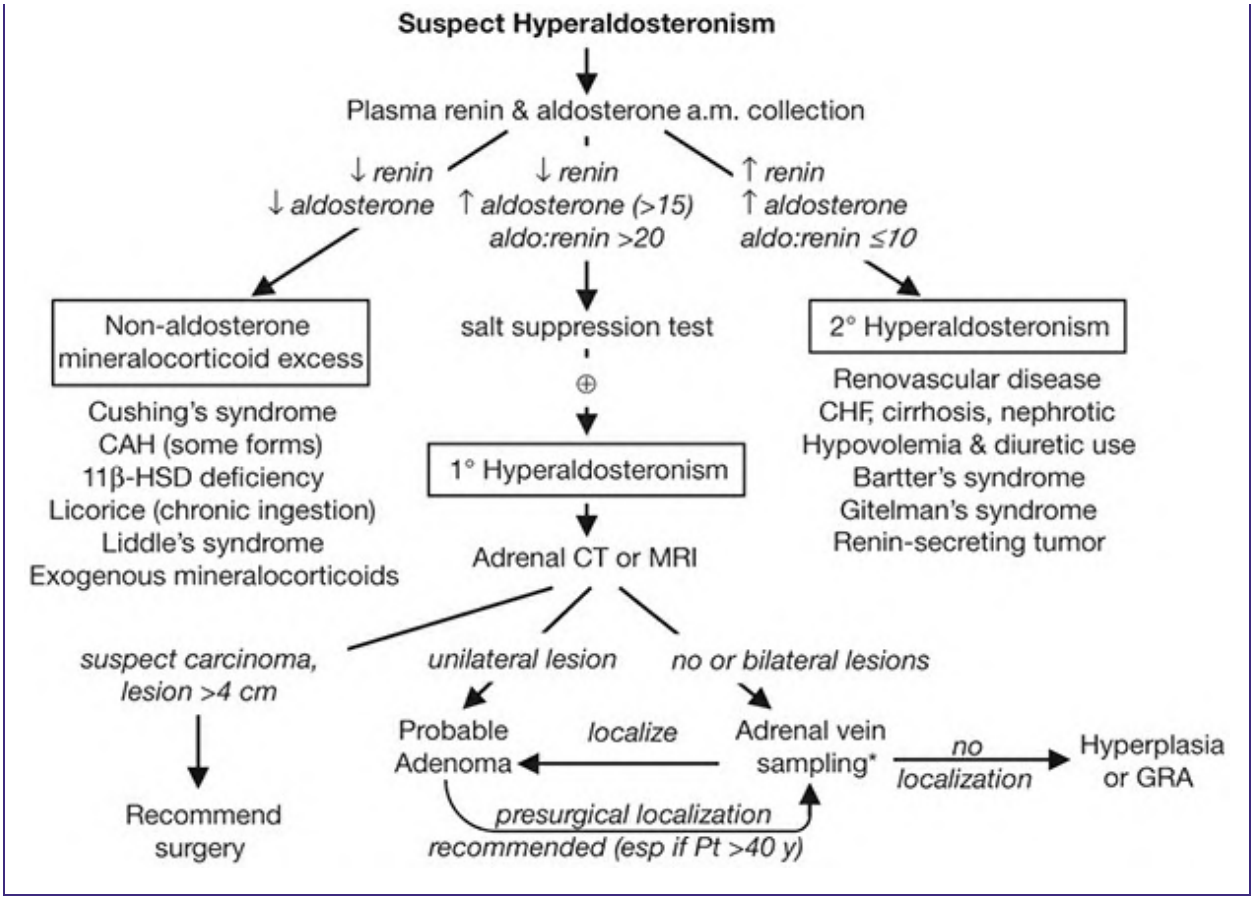
Clinical manifestations

- **Mild-to-mod. HTN**: 2–6% of all HTN, >10% of refractory cases (*J Human HTN* 2024;38:8)
- Headache, muscle weakness, polyuria, polydipsia; no peripheral edema because of "escape" from Na retention; malignant HTN is rare
- Classically **hypokalemia** (but often normal), metabolic alkalosis

Diagnosis (*JCEM* 2016;101:1889; *Endo Metab Clin* 2019;48:681; *J Clin Endo Met* 2021;106:2423)

- 5–10% of Pts w/ HTN; ∴ screen if HTN + hypoK, adrenal mass, refractory/early onset HTN
- Screening: ↓↓ renin, **aldo** >15–20 ng/dL, **plasma aldo:renin ratio** (>20 if 1°); obtain 8 a.m. paired values (*off* spirono & eplerenone for 6 wk); cut-offs arbitrary; Se var., Sp >70%
- ACEI/ARB, diuretics, CCB can ↑ renin activity → ↓ PAC/PRA ratio and βBs may ↑ PAC/PRA ratio; ∴ avoid. α-blockers generally best to control HTN during dx testing.
- Confirm with **sodium suppression test** (fail to suppress aldo after sodium load) oral salt load (+ KCl) × 3 d, ✓ 24-h urine (⊕ if urinary aldo >12 µg/d while urinary Na >200 mEq/d) or 2 L NS over 4 h, measure plasma aldo at end of infusion (⊕ if aldo >5 ng/dL)

Figure 7-4 Approach to suspected hyperaldosteronism



*Even if nodule seen c/f PAH, still must do AVS to r/o hyperplasia in other adrenal w/ incidental non-fxnal nodule

Treatment (*SCNA* 2014;94:643)

- Adenoma → adrenalectomy vs. medical Rx w/ spironolactone or eplerenone
- Hyperplasia → spironolactone or eplerenone; GRA → glucocorticoids ± spironolactone
- Carcinoma → adrenalectomy

Adrenal Insufficiency

Etiologies

- **Primary** = adrenocortical disease = ***Addison's disease***
  autoimmune: isolated or in assoc w/ APS (see table on page 7-2)
  infection: TB, CMV, histoplasmosis, paracoccidioidomycosis
  vascular: hemorrhage (usually in setting of sepsis), adrenal vein thrombosis, HIT, trauma
  metastatic disease: (90% of adrenals must be destroyed to cause insufficiency)
  deposition diseases: hemochromatosis, amyloidosis, sarcoidosis
  drugs: azole antifungals, etomidate (even after single dose), rifampin, anticonvulsants
- **Secondary** = pituitary failure of ACTH secretion (but adrenal **aldosterone intact** b/c RAA axis) any cause of primary or secondary hypopituitarism (see "Pituitary Disorders") glucocorticoid therapy (most likely to occur after >3–4 wks of Rx, even with doses <10 mg/d; avoid by slow taper over wks [*Eur J Endo* 2024;190:G25]); megestrol

Clinical manifestations (*Lancet* 2021;397:613)

- **Primary or secondary: weakness and fatigability** (95%), **weight loss** (70%), **orthostatic**

hypotension (60%), nausea (50%), vomiting (50%), hyponatremia (75%)
- **Primary only** (extra s/s due to lack of aldosterone and ↑ ACTH): **hyperkalemia,** marked **orthostatic hypotension** (because volume depleted), salt craving, **hyperpigmentation** (seen in skin creases, mucous membranes, pressure areas, nipples)
- **Secondary only:** ± other manifestations of hypopituitarism (see "Pituitary Disorders")

Diagnostic studies (*JCEM* 2016;101:364; *J Endocr Soc* 2021;8:22)

- **Cosyntropin (ACTH) stimulation test** (testing ability of 250 µg ACTH → ↑ cortisol)
  - normal = 60-min (or 30-min) post-ACTH cortisol ≥15 µg/dL
  - abnormal in *primary* b/c adrenal gland diseased and unable to give adequate output
  - abnormal in *chronic* secondary b/c adrenals atrophied and unable to respond
  - may be *normal* in the rare *acute pituitary injury* b/c adrenals still able to respond → use early a.m. cortisol instead
  - All glucocorticoids (incl creams, inh, drops, & intra-articular) affect baseline cortisol. Must know exposure to interpret. Cortisol thresholds not reliable in Pts with high or low cortisol-binding proteins (eg, women on OCP, severe hypoalbuminemia).
- Without stimulation, early a.m. serum cortisol: <3 µg/dL virtually diagnostic (except for hospitalized Pts) (*Clin Endo* 2022;9:21); ≥15 excludes chronic AI
- Other tests (w/ guidance by endocrinologist): renin, aldosterone, insulin-induced hypoglycemia (measure serum cortisol response); metyrapone (blocks cortisol synthesis and therefore stimulates ACTH, measure plasma 11-deoxycortisol and urinary 17-hydroxycorticosteroid levels)
- Other lab abnormalities: hypoglycemia, eosinophilia, lymphocytosis, ± neutropenia
- ACTH: ↑ in 1°, ↓ or low-normal in 2°
- Imaging studies to consider after biochemical diagnosis firm
  - pituitary MRI to detect anatomic abnormalities
  - adrenal CT: small, noncalcified adrenals in autoimmune, enlarged in metastatic disease, hemorrhage, infection or deposition (although they may be normal-appearing)

Treatment

- *Acute* insufficiency: volume resusc. w/ normal saline + **hydrocortisone IV** (vide infra)
- *Chronic* insufficiency: (1) prednisone ~4–5 mg PO qam or hydrocort 15–25 mg PO qd ($^2/_3$ a.m., $^1/_3$ early p.m.); (2) fludrocort (*not* needed in 2° adrenal insufficiency) 0.05–0.2 mg PO qam (*JCEM* 2018;103:376); (3) backup hydrocort 100 mg prefilled IM for emergencies

Adrenal insufficiency & critical illness (*NEJM* 2003;348:727; *JAMA* 2009;301:2362)

- Low cortisol-binding proteins; ∴ dx of adrenal insufficiency problematic (*NEJM* 2013;368:1477)
- Adrenal insufficiency rare in most cases of shock unless adrenal infarction or bleed, Waterhouse–Friderichsen, CNS or pituitary bleed
- Reasonable to test for adrenal insufficiency if high suspicion in hypotensive Pt
- Can consider above dx criteria, but decision for Rx should also be based on clinical assessment due to risk of false ⊖ and ⊕ results in context of altered physiology
- If concerned, start steroids early: hydrocortisone 100 mg IV followed by 50 mg IV q6h

Adrenal crisis in adrenal insufficiency (*NEJM* 2019;381:852)

- Precipitants: preexisting adrenal insufficiency + serious infection or GI illness, bilateral adrenal hemorrhage or infarction, pituitary infarction; treatment of profound hypothyroidism w/ levothyroxine admin. before steroids (if concomitant untreated adrenal insufficiency)
- Presentation: shock + anorexia, N/V, abd pain, weakness, fatigue, confusion, coma, fever
- Lab findings: hyponatremia, hyperkalemia (1°)
- Rx: hydrocortisone 100 mg IV followed by 50 mg IV q6 + IVF; do not delay for dx tests

Pheochromocytoma & Paraganglioma

Clinical manifestations (*NEJM* 2019;381:552)

- Neuroendocrine neoplasm leads to inappropriate and paroxysmal release of adrenergic agents including epinephrine, norepinephrine, and rarely dopamine
- **Classic triad of 3Ps**: episodic headaches (pain), palpitations, and perspiration; only 50% have paroxysmal hypertension and most Pts do *not* have three classic sx
- Paroxysms can be triggered by meds (eg, β-blockers), abdominal manipulation
- Up to 40% of pheos/paragangliomas (= extra-adrenal pheo) thought to have underlying genetic etiology; genetic testing frequently recommended
- Associated with MEN2A/2B, von Hippel Lindau, NF1, familial paraganglioma (mutations in succinate dehydrogenase gene B, C, and D), *MAX* or *TMEM127* mutations

Diagnostic studies (*JCEM* 2014;99:1915)

- Plasma fractionated metanephrines: 97% Se, 91% Sp. Screening test of choice if high risk, but ↑ rate of false ⊕ in low-prevalence population. False ⊕ rate lower if patient supine for 30 min (estimated 2.8× ↑ false ⊕ if seated).
- 24° urinary fractionated metanephrines: 98% Se, 98% Sp. Screening test of choice if low risk (b/c false ⊕ with severe illness, renal failure, OSA, labetalol due to assay interference, acetaminophen, TCAs, medications containing sympathomimetics).
- Adrenal CT or T2-weighted MRI; PET for known metastatic disease or to localize nonadrenal mass but usually easy to find; consider MIBG scintigraphy if CT/MRI ⊖
- Consider genetic panel testing in all Pts (*J Intern Med* 2019;285:187)

Treatment

- α-blockade first (phenoxybenzamine/doxazosin) ± β-blockade (propranolol) → surgery
- Preoperative volume expansion is critical due to possible hypotension after tumor excision

Adrenal Incidentalomas

Epidemiology

- 4% of Pts undergoing abdominal CT scan have incidentally discovered adrenal mass; prevalence ↑ with age

Differential diagnosis

- **Nonfunctioning mass:** adenoma, cysts, abscesses, granuloma, hemorrhage, lipoma, myelolipoma, primary or metastatic malignancy
- **Functioning mass:** pheochromocytoma, adenoma (cortisol, aldosterone, sex hormones), other endocrine tumor, carcinoma

Hormonal workup (*EJE* 2016;175:G1; *NEJM* 2021;384:1542)

- **Rule out subclinical Cushing's syndrome** *in all Pts* using 1 mg overnight DST (Sp 91%) and obtaining baseline DHEA-S. Abnormal results require confirmatory testing.
- **Rule out hyperaldosteronism** *if hypertensive* w/ plasma aldo & renin (vide supra)
- **Rule out pheochromocytoma** *in ALL Pts* (b/c of morbidity unRx'd pheo) using plasma fractionated metanephrines; if positive check 24-h urine fractionated metanephrines
- **Rule out other hormone secretion** depending on Pt's presenting sx with: testosterone, DHEA-S, estradiol, 17-hydroxyprogesterone (if concerned for congenital adrenal hyperplasia)

Malignancy workup

- CT and MRI characteristics may suggest adenoma vs. carcinoma
  Benign features: unenhanced CT <10 Hounsfield units or CT contrast-medium washout >50% at 10 min; size <4 cm; smooth margins, homogenous and hypodense appearance; can follow such incidentalomas w/ periodic scans
  Suspicious features: size ≥4 cm or ↑ size on repeat scan; >10 Hounsfield units on CT, irregular margins, heterogeneous, dense or vascular appearance; h/o malignancy or young age. Such incidentalomas warrant resection or repeat scan at short interval.
- Rule out metastatic cancer (and infection) in Pts w/ h/o cancer; ~50% of adrenal incidentalomas are malignant

Follow-up

- If hormonal workup ⊖ and appearance benign, need for further follow-up imaging controversial (*Annals* 2019;171:107)

CALCIUM DISORDERS

Laboratory Findings in Calcium Disorders

Ca	PTH	Disease	PO_4	25-(OH)D	$1,25\text{-}(OH)_2D$
↑	↑ or ULN	Hyperparathyroidism (1° and 3°)	↓	↓ to nl	nl to ↑
	↑ or nl	Familial hypocalciuric hypercalcemia	↓	var.	nl
	↓	Malignancy	var.	var.	var.
		Vitamin D excess	↑	↑↑	nl to ↑
		Milk-alkali syndrome, thiazides	var.	var.	var.
		↑ Bone turnover	nl to ↑	var.	nl
↓	↑↑	Pseudohypoparathyroidism	↑	var.	↓
	↑	Vitamin D deficiency	↓	↓↓	nl/↓
		Chronic renal failure (2° hyperpara)	nl to↑	var.	↓
	var.	Acute calcium sequestration	var.	var.	var.
	↓	Hypoparathyroidism	↑	var.	↓ to nl

Pitfalls in measuring calcium

- Physiologically active Ca is free or ionized (iCa). Serum Ca reflects total calcium (bound + unbound) and ∴ influenced by albumin (main Ca-binding protein).
- Corrected Ca (mg/dL) = measured Ca (mg/dL) + {0.8 × [4 – albumin (g/dL)]}
- Alkalosis will cause more Ca to be bound to albumin (∴ total Ca may be normal but ↓ iCa)
- Best to measure **ionized Ca directly** (*but accuracy is lab dependent*)

HYPERCALCEMIA

Etiologies of Hypercalcemia (*JAMA* 2022;328:1624)

Category	Etiologies

Hyperparathyroidism (HPT) (*NEJM* 2018;379:1050; *Lancet* 2018;391:168)	**1°: adenoma** (85%), hyperplasia (15–20%; spont. vs. MEN1/2A), carcinoma (<1%), meds (Lithium → ↑ PTH) **3°:** after long-standing 2° hyperparathyroidism (as in renal failure) → autonomous nodule develops, requires surgery
Familial hypocalciuric hypercalcemia (FHH)	Inact. mut. in Ca-sensing receptor (FHH1), Gα11 (FHH2), AP2S1 (FHH3) → ↑ Ca set point; ± mild ↑ PTH Acquired form due to autoAb vs. Ca-sensing receptor (rare) FE_{Ca} [(24-h U_{Ca}/serum Ca)/(24-h U_{Cr}/serum Cr)] <0.01
Malignancy (*NEJM* 2022;386:1443)	PTH-related peptide (PTHrP) → humoral ↑ Ca of malignancy (eg, squamous cell cancers, renal, breast, bladder) Cytokines → ↑ osteoclast activity (eg, hematologic malig) ↑ 1,25-$(OH)_2$D (eg, rare lymphomas) Local osteolysis (eg, breast cancer, myeloma)
Vitamin D excess	Granulomas (sarcoid, TB, histo, GPA) → ↑ 1-OHase → ↑ 1,25-$(OH)_2$D. Vitamin D intoxication.
↑ **Bone turnover**	Hyperthyroidism, immobilization + Paget's disease, vit A excess
Miscellaneous	Thiazides; excessive Ca-based antacids or massive dairy consumption (milk-alkali syndrome); adrenal insufficiency
Among inPts w/ hypercalcemia: 45% have cancer, 25% 1° HPT, 10% CKD → 3° HPT	

Clinical manifestations ("bones, stones, abdominal groans, and psychic moans")

- **Hypercalcemic crisis** (usually when Ca >13–15): polyuria, dehydration, Δ MS
  - Ca toxic to renal tubules → blocks ADH activity, causes vasoconstriction and ↓ GFR → polyuria but Ca reabsorption → ↑ serum Ca → ↑ nephrotoxicity and CNS sx
- Osteopenia, fractures, and osteitis fibrosa cystica (latter seen in severe hyperpara. only → ↑ osteoclast activity → cysts, fibrous nodules, salt & pepper appearance on X-ray)
- Nephrolithiasis, nephrocalcinosis, nephrogenic DI
- Abdominal pain, anorexia, nausea, vomiting, constipation, pancreatitis, PUD
- Fatigue, weakness, depression, confusion, coma, ↓ DTRs, short QT interval
- 1° HPT: 80% asx, 20% nephrolithiasis, osteoporosis, etc.

Diagnostic studies

- Hyperparathyroidism (HPT) and malignancy account for 90% of cases of ↑ Ca; HPT more likely if asx or chronic; malignancy (usually overt) more likely if acute or sx
- Ca, alb, iCa, PTH (may be inapprop. normal in 1° HPT & FHH; *JAMA* 2014;312:2680), PO_4
  - ↑ or high nl PTH: Ca/Cr clearance ratio <0.01 → FHH
  - ↓ PTH: ✓ PTHrP, Aϕ, & search for malig (eg, CT, mammo, SPEP/UPEP) and ✓ vit D: ↑ 25-(OH)D → meds; ↑ 1,25-(OH)2D → granuloma (✓ CXR, ACE, r/o lymph)

Acute Treatment of Severe Hypercalcemia (*BMJ* 2015;350:h2723)

Treatment	Onset	Duration	Comments
Normal saline (4–6 L/d)	h	during Rx	Natriuresis → ↑ renal Ca excretion
± **Furosemide**	h	during Rx	Use cautiously, only if volume overloaded
IV Bisphosphonates	1–2 d	var.	Inhibit osteoclasts, useful in malignancy; caution in renal failure; risk of jaw osteonecrosis; monitor for hypoCa; should consider in

			Pts w/ new fx prior to discharge
Calcitonin	h	~48 hrs	Bridging Rx, quickly develops tachyphylaxis
Glucocorticoids	days	days	Useful in some malig, granulomatous disorders, & vitamin D intox.
Denosumab (*JCEM* 2014;99:3144)	days	months	Monoclonal Ab against RANKL; typically used in hyperCa of malignancy; not renally cleared
Hemodialysis	min	during Rx	If other measures ineffective or contraindicated

Treatment of 1° HPT (including asymptomatic) (*JBMR* 2022;37:2290)

- Surgery if: age <50 y; serum Ca >1 mg/dL >ULN; CrCl <60 mL/min, hypercalciuria, DEXA T score < −2.5
- If surgery declined/deferred, can Rx with cinacalcet (↓ Ca & PTH but may not ↑ BMD)
- If not yet candidate for surgery: ✓ serum Ca & Cr annually and BMD q2y

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Hypocalcemia

Etiologies of Hypocalcemia	
Category	**Etiologies**
Hypoparathyroidism (*NEJM* 2019;380:1738; *JBMR* 2022;37:2630)	Iatrogenic (s/p thyroidectomy, rarely after parathyroidectomy); sporadic; familial (APS1, activating Ca-sensing receptor mutations; see page 7-2); Wilson's, hemochromatosis; hypoMg (↓ secretion and effect); activating Ca-sensing receptor autoAb
Pseudo-hypoparathyroidism (*Endo Metab Clin North Am* 2018;47:865)	1a, 1b, & 1c: PTH end-organ resistance (∴ ↑ serum PTH) 1a & 1c: + skeletal abnl, short stature, & developmental delay Pseudopseudohypoparathyroidism = 1a mutation inherited from father, no hormonal abnormalities
Vit D defic. or resist (*NEJM* 2011;364:248; *JCEM* 2012;97:1153)	Nutritional/sunlight deprivation; GI disease/fat malabs.; drugs (anticonvulsants, rifampin, ketoconazole, 5-FU/leucovorin); genetic (1α-hydroxylase, VDR mutations). Deficiency more common.
Chronic renal failure	↓ 1,25-$(OH)_2$D production from elevated FGF23, ↑ PO_4 from ↓ clearance
Accelerated net bone formation	Post-parathyroidectomy, Paget's disease (*JBMR* 2019;34:579), osteoblastic metastases
Calcium sequestration	Pancreatitis, citrate excess (after blood transfusions), acute ↑↑ PO_4 (ARF, rhabdomyolysis, tumor lysis), bisphosphonates

Clinical manifestations

- **Neuromuscular irritability:** perioral paresthesias, cramps, ⊕ **Trousseau's** (inflation of BP cuff ≥3 min → carpal spasm), ⊕ **Chvostek's** (tapping facial nerve → contraction of facial muscles), laryngospasm; irritability, depression, psychosis, seizures, ↑ QT
- Rickets and/or osteomalacia: chronic ↓ vit D → ↓ Ca, ↓ PO_4 → ↓ bone/cartilage mineralization, growth failure, bone pain, muscle weakness
- **Renal osteodystrophy**: osteomalacia [↓ mineralization of bone due to ↓ Ca and 1,25- $(OH)_2$D] & osteitis fibrosa cystica (due to ↑ PTH), adynamic bone disease or mixed uremic osteodystrophy; dx by bone biopsy

Diagnostic studies

- Ca, alb, iCa, PTH, 25-(OH)D, 1,25-(OH) $_2$D (if renal failure or rickets), Cr, Mg, PO_4, Aφ, U_{Ca}

Treatment (also treat concomitant vitamin D deficiency; *Endocrine* 2020;69:485)

- Severely symptomatic: Ca gluconate (1–2 g IV over 20 min) + oral Ca + calcitriol (but takes hrs to work) ± Mg (50–100 mEq/d); 10% $CaCl_2$ in codes or via CVL
- Consider Ca gtt or PO to follow b/c effect of IV bolus typically lasts only a few hours
- Chronic (depends on etiol.): oral Ca (1–2 g/d; citrate better absorbed than carbonate, esp. if achlorhydria or on PPI) and typically calcitriol (0.25–2 µg/d), and replete vit. D defic. Consider thiazide to ↓ U_{Ca} or PTH analogues (eg, palopegteriparatide in hypopara).
- Chronic renal failure: phosphate binder(s), oral Ca, calcitriol, or analogue

DIABETES MELLITUS

Definition (*Diabetes Care* 2025;48:S27)

- Either Hb_{A1c} ≥6.5, fasting glc ≥126 mg/dL, or glc 2 h after OGTT ≥200 mg/dL × 2 (for any test) or single random glc ≥200 mg/dL w/ classic sx of hyperglycemia
- Blood glc higher than normal, but not frank DM ("prediabetes," ~40% U.S. population)
  Hb_{A1c} 5.7–6.4%, impaired fasting glc (IFG) 100–125 mg/dL, or 2 h prandial glc 140–199
  Preventing progression to DM: diet/exercise (58% ↓), metformin (31% ↓); GLP-1RA

Categories

- **Type 1** (*Lancet* 2018;391:2449): islet cell destruction; absolute insulin deficiency; ketosis in absence of insulin; prevalence 0.4%; usual onset in childhood but can occur throughout adulthood; ↑ risk if ⊕ FHx; HLA associations; anti-GAD, anti-islet cell, & anti-insulin autoAb
- **Type 2** (*Lancet* 2017;389:2239): insulin resistance + relative insulin ↓; prevalence 6%; onset generally later in life; no HLA assoc.; risk factors: age, ⊕ FHx, obesity, sedentary lifestyle
- **Type 2 DM p/w DKA** ("ketosis-prone diabetes" or "Flatbush diabetes"): most often seen in nonwhite, ± anti-GAD Ab, eventually may not require insulin (*Endo Rev* 2008;29:292)
- **Type 3c** (pancreatogenic)**:** α & β cell destruction 2/2 pancreatitis, hemochromatosis, CF, etc.
- **M**ature-**O**nset **D**iabetes of the **Y**oung (**MODY**): autosomal dom. forms of DM due to defects in insulin secretion genes; genetically and clinically heterogeneous (*JCEM* 2021;106:237)
- **2° causes:** exogenous glucocorticoids, glucagonoma (3 Ds = DM, DVT, diarrhea), endocrinopathies (Cushing's, acromegaly), gestational, drugs (PI, atypical anti-ψ)

Clinical manifestations

- Polyuria, polydipsia, polyphagia with unexplained weight loss; may be asymptomatic

Diabetes Treatment Approach for Pt w/ ASCVD, HF, or CKD	
Med (↓ Hb_{A1C})	**Comments**
GLP-1 receptor agonists (~1–2%)	↑ glc-depend. insulin secretion. Delay gastric emptying. Wt ↓, N/V. ↓ CVD/MI/stroke, esp. if ASCVD. Improve PAD. ↓ prog of CKD. *1st line* if est. ASCVD or high ASCVD risk (age >55, LVH, arterial stenosis >50%), *regardless of A1c* Dual glc-dependent insulinotropic polypeptide & GLP-1R agonists (eg,

	tirzepatide) w/ greater ↓ in A1C & wt (*NEJM* 2021;385:503)
SGLT2 inhibitors (~0.5–1%)	↑ glucosuria. Wt ↓. ↑ genital infxn. ? caution if PAD. ↓ CVD/HHF. ↓ prog. of renal disease. ± ↓ MI if ASCVD. *1st line* if HF, proteinuric CKD, *regardless of A1c*
Metformin (~1–1.5%)	↓ hepatic gluconeogenesis. Mild wt ↓. Rare lactic acidosis. Caution if GFR 30–45; contra. if <30. Poss CV benefit. Historically 1st line Rx, although debate given benefit of above Rx's
Additional Diabetes Treatment Options	
DPP-4 inhibitors (~0.5–1%)	Block degrad. GLP-1 & GIP → ↑ insulin. ↑ risk of HF w/ saxagliptin (*NEJM* 2013;369:1317), not w/ others
Sulfonylureas (SU) (~1.5%)	↑ insulin secretion. Hypoglycemia; wt gain. Hastens β-cell burnout.
Thiazolidinediones (TZD) (~1%)	↑ insulin sens. in adipose & muscle. Wt ↑, fluid retention & CHF. Hepatox. ↓ MACE w/ pioglitazone (*BMJ Open* 2017;7:e013927). Contraindic. in HF & liver dysfxn.
Glinides (~1%)	↑ insulin secretion; hypoglycemia; wt gain
α-gluc. inhib (~0.5%)	↓ intestinal carbohydrate absorption. Abd pain, flatulence.
Pramlintide (~0.5%)	Delays gastric emptying & ↓ glucagon. N/V.
Insulin (variable)	↓↓ gluc; wt gain. Mandatory in T1D; consider in T2D if oral Rx inadeq. Pump system in T1D w/ better control (*NEJM* 2022;387:869).
Gastric bypass	Wt ↓↓↓; can cause remission DM (*NEJM* 2014;370:2002)

Lifestyle changes including weight management are foundational. (*Diabetes Care* 2025;48:S167; *NEJM* 2021;385:896; *NEJM* 2019;381:1995; *Lancet* 2019;393:31; *Circ* 2019;139:2022; *NEJM* 2019;380:2295 & 2025;392:2001)

Insulin Preparations (*Diabetes Care* 2025;48:S181)

Type (Example)	Onset	Peak	Duration	Comments
Ultrarapid (Fiasp, Lyumjev)	10–15 min	1–2 h	3–5 h	Give 10 min before meal
Rapid (lispro, aspart)	15–25 min	1–2 h	3–5 h	Give 15 min before meal
Short (regular)	~30 min	2–3 h	5–8 h	Give ~30 min before meal
Intermed. (NPH)	2–3 h	4–8 h	10–14 h	Can cause protamine Ab prod
Long (glargine, detemir)	1–2 h	n/a	12–24 h	Once-daily basal insulin

Complications (*CJASN* 2017;12:1366)

- **Retinopathy**
  nonproliferative: "dot & blot" and retinal hemorrhages, cotton-wool/protein exudates
  proliferative: neovascularization, vitreous hemorrhage, retinal detachment, blindness
  treatment: photocoagulation, surgery, intravitreal bevacizumab injections
- **Nephropathy:** microalb. → proteinuria ± nephrotic syndrome → renal failure. ACEI/ARB, SGLT2i, GLP-1RA, & finerenone (*NEJM* 2020;383:1436 & 2219; 2024;391:109); low-protein diet.
- **Neuropathy:** *peripheral:* symmetric distal sensory loss, paresthesias, ± motor loss
  autonomic: gastroparesis, constipation, neurogenic bladder, erectile dysfxn, orthostasis
  mononeuropathy: sudden-onset peripheral or CN deficit (footdrop, CN III > VI > IV)
- **Accelerated atherosclerosis:** coronary, cerebral, and peripheral arterial beds
- **Infections:** UTI, osteomyelitis of foot, candidiasis, mucormycosis, necrotizing external otitis

- **Dermatologic:** necrobiosis lipoidica diabeticorum, lipodystrophy, acanthosis nigricans

Outpatient screening and treatment goals (*Diabetes Care* 2025;48:S128 & S207)

- ✓ Hb_{A1C} q3–6mo, goal <7% for most Pts. Goal <6.5% if low-risk hypoglycemia; ≤8% if h/o severe hypoglycemia, elderly, or other comorbid. Tighter control required in preg. to prevent maternal & fetal complications; goal Hb_{A1C} <6.0–6.5% and FBG <95 mg/dL.
- Microvascular complic. (nephropathy, retinopathy, neuropathy) ↓↓ by strict glycemic control
- Macrovascular complications (ASCVD) also ↓ by strict control, but benefit takes longer to emerge (*NEJM* 2015;372:2197) and some concern re: hypoglycemia (*Lancet* 2009;373:1765)
- Microalbuminuria screening yearly with spot microalbumin/Cr ratio, goal <30 mg/g
- Wt loss (dietary/drugs) can regress or resolve DM (*Endo Rev* 2018;39:79; *NEJM* 2018;379:1107)
- **BP** ≤130/80, consider targeting SBP ~120 s (*NEJM* 2025;392:1155); benefit of ACEI/ARB
- **Lipids:** statin initiation in all diabetics age 40–75 if LDL-C >70 (see "Lipid Disorders")
- ASA in 2° prevention; ? role in 1°, balancing ↓ MACE & ↑ bleeding (*NEJM* 2018;379:1529)
- Dilated retinal exam and comprehensive foot exam

Management of hyperglycemia in inPts

- Identify reversible causes/precipitants (dextrose IVF, glucocorticoids, post-op, ↑ carb diet)
- Dx studies: BG fingersticks (fasting, qAC, qHS; or q6h if NPO), Hb_{A1C}
- Treatment goals: avoid hypoglycemia, extreme hyperglycemia (>180 mg/dL)
- Transition to inPt: T1D: do not stop basal insulin (can → DKA)
  T2D: stopping oral DM meds generally preferred to avoid hypoglycemia or med interaction (except if short stay, excellent outPt cntl, no plan for IV contrast, nl diet)
  If Pt on insulin as outpt do not rely on sliding scale alone (*Diabetes Care* 2022;45:S244)
  If on insulin pump, consult Endocrinology for guidance on pump mgmt
- Starting new insulin regimen
  Basal = 0.2–0.4 U/kg/d NPH q12h or detemir or glargine
  + correction insulin for BG >150 mg/dL
  + prandial insulin if eating: 0.05–0.1 U/kg/meal lispro, aspart, or regular
- *When NPO*
  T1D: continue basal insulin at current dose or 75% depending on BG control
  T2D: continue basal insulin at 25–75% depending on BG control and level of insulin resistance. Hold all prandial insulin.
- In ICU: targeting glc 140–180 mg/dL reasonable (*NEJM* 2023;389:1180)
- Discharge regimen: similar to admission regimen unless poor outPt cntl or strong reason for Δ. Arrange early insulin and glucometer teaching, prompt outPt follow-up.

Diabetic Ketoacidosis (DKA)

Precipitants (the I's)

- **Insulin defic.** (ie, failure to take enough insulin); **Iatrogenesis** (glucocorticoids; SGLT2 inhibitors—can be w/o marked hyperglycemia; *Diabetes Care* 2016;39:532)
- **Infection** (pneumonia, UTI) or **Inflammation** (pancreatitis, cholecystitis)
- **Ischemia** or **Infarction** (myocardial, cerebral, gut); **Intoxication** (alcohol, drugs)

Pathophysiology (*NEJM* 2015;372:546)

- Occurs in **T1D** (and in ketosis-prone T2D); ↑ glucagon and ↓ insulin
- Hyperglycemia due to: ↑ gluconeogenesis, ↑ glycogenolysis, ↓ glucose uptake into cells
- Ketosis due to: insulin deficiency → mobilization and oxidation of fatty acids, ↑ substrate for ketogenesis, ↑ ketogenic state of the liver, ↓ ketone clearance

Clinical manifestations (*Diabetes Care* 2009;32:1335 & 2016;39:S99)

- Polyuria, polydipsia, & dehydration → ↑ HR, HoTN, dry mucous membranes, ↓ skin turgor
- N/V, abdominal pain (either due to intra-abdominal process or DKA), ileus
- Kussmaul's respirations (deep) to compensate for metabolic acidosis with odor of acetone
- Δ MS → somnolence, stupor, coma; mortality ~1% even at tertiary care centers

Diagnostic studies

- ↑ **Anion gap metabolic acidosis** (pH <7.3 & HCO_3 <18): can later develop nonanion gap acidosis due to urinary loss of ketones (HCO_3 equiv.) & fluid resuscitation w/ chloride
- **Ketosis:** ⊕ **urine and serum ketones** (predominant ketone is β-OH-butyrate, but acetoacetate measured by assay; urine ketones may be ⊕ in fasting normal Pts)
- ↑ Serum glc usually >250 mg/dL (but can be euglycemic if on SGLT2i); ↑ BUN & Cr
- Hyponatremia: corrected Na = measured Na + [2.4 × (measured glc – 100)/100]
- ↓ or ↑ K (but even if serum K is elevated, *usually total body K depleted*); ↓ total body phos
- Leukocytosis & ↑ amylase (even if no pancreatitis)

Treatment of DKA (*BMJ* 2019;365:1114)	
R/o possible precipitants	Infection, intra-abdominal process, MI, etc. (vide supra)
Aggressive hydration	1 L NS then ~250 mL/hr, tailor to dehydration & CV status
Insulin	0.1 U/kg bolus followed by 0.1 U/kg/h IV Continue insulin drip until AG normal If glc <250 and AG still high → add dextrose to IVF and ↓ insulin drip to 0.02–0.05 U/kg/hr AG nl & can eat → SC insulin (overlap IV & SC 2–3 h)
Electrolyte repletion	K: add 20–40 mEq/L IVF if serum K <5.4; insulin promotes K entry into cells → hold insulin if K <3.3. Careful K repletion in Pts with renal failure. HCO_3: consider repletion if pH <6.9 or if cardiac instability

Hyperosmolar Hyperglycemic State

Definition, precipitants, pathophysiology (*Med Clin North Am* 2017;101:587)

- Extreme hyperglycemia (w/o ketoacidosis) + hyperosm. + Δ MS in T2D (typically elderly)
- Precip same as for DKA, but also include dehydration and renal failure
- Hyperglycemia → osmotic diuresis → vol depletion → prerenal azotemia → ↑ glc, etc.

Clinical manifestations & dx studies (*Diabetes Care* 2014;37:3124)

- Volume depletion and Δ MS
- ↑ **serum glc** (usually >600 mg/dL) and ↑ **meas. serum osmolality** (>320 mOsm/L) effective Osm = 2 × Na (mEq/L) + glc (mg/dL)/18
- pH >7.3, no ketoacidosis; usually ↑ BUN & Cr; [Na] depends on glucose & dehydration

Treatment

- Rule out possible precipitants; ~15% mortality due to precipitating factors
- **Aggressive hydration:** initially NS, then ½ NS, average fluid loss up to 8–10 L. *Prioritize*

adequate hydration before insulin initiation if not in concomitant DKA.

- **Insulin** (eg, 10 U IV followed by 0.05–0.1 U/kg/h), target glucose ~250 until Pt alert

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Hypoglycemia

Clinical manifestations (glucose <~55 mg/dL)

- **CNS:** headache, visual Δs, Δ MS, weakness, seizure, LOC (neuroglycopenic sx)
- **Autonomic:** diaphoresis, palpitations, tremor (adrenergic sx)

Etiologies

- **Pts w/ diabetes**: excess insulin, oral hypoglycemics, missed meals, renal failure (↓ insulin & SU clearance); β-blockers can mask adrenergic symptoms of hypoglycemia
- **Pt without diabetes**: low fasting glucose w/o sx can be normal
  - ↑ **insulin:** exogenous insulin, sulfonylureas, insulinoma, anti-insulin antibodies
  - ↓ **glucose production:** hypopituitarism, adrenal insufficiency, glucagon deficiency, hepatic failure, renal failure, CHF, alcoholism, sepsis, severe malnutrition
  - **Postprandial**, esp. postgastrectomy or gastric bypass: excessive response to glc load
  - ↑ **IGF-II:** non-islet tumor (rare)

Evaluation in patients without diabetes (*JCEM* 2009;94:709)

- If clinically ill: take measures to avoid recurrent hypoglycemia; ✓ BUN, Cr, LFTs, TFTs, prealbumin; IGF-I/IGF-II ratio when appropriate
- If otherwise healthy: 72-h fast w/ monitored blood glc; stop for neuroglycopenic sx
- *At time of hypoglycemia:* insulin, C peptide (↑ w/ insulinoma and sulfonylureas, ↓ w/ exogenous insulin), β-OH-butyrate, sulfonylurea levels
- At end of fast, give 1 mg glucagon IV and measure response of plasma glc before feeding. *Rising glucose (>30 mg/dL) s/p glucagon admin suggests residual glycogen stores (inconsistent with starvation physiology s/p 72-hour fast); often seen in insulinoma.*

Treatment

- Glucose tablets, paste, & fruit juice are first-line Rx for Pts who can take POs
- 25–50 g of D_{50} IV; if no access, glucagon 0.5–1 mg IM or SC (side effect: N/V)

LIPID DISORDERS

Measurements

- Lipoproteins = lipid core (cholesteryl esters & triglycerides) + phospholipid surface + proteins. Include: chylomicrons, VLDL, IDL, LDL, HDL, Lp(a).
- LDL-C typically estimated: LDL-C = TC – HDL-C – (TG/5), ∴ ideally measure fasting. Inaccurate if TG >400 or LDL-C <70; ∴ use Martin–Hopkins or NIH eq or directly measure. Levels stable up to 24 h after ACS, then ↓ and may take 6 wk to return to nl.
- PEx clues: tendon xanthomas (eg, Achilles), imply LDL >300 mg/dL; eruptive xanthomas on extensor surfaces imply TG >1500 mg/dL; xanthelasma (yellowish streaks on eyelids)
- Metabolic syndrome (≥3 of following): waist ≥40″ (♂) or ≥35″ (♀); TG ≥150 mg/dL; HDL <40 (♂) or <50 mg/dL (♀); BP ≥130/85 mmHg; fasting glc ≥100 mg/dL (*Circ* 2009;120:1640)
- Lp(a) = LDL particle + apo(a); concentration genetically determined; a/w CAD & AS

Dyslipidemias

- 1° (inherited causes): *familial hyperchol.* (1:250): defective LDL receptor; ↑↑ chol; ↑ CAD; *familial hyperTG*: ↑ TG & pancreatitis; *familial combined hyperlipid.:* ↑ chol & TG; etc.
- 2°: DM (↑ TG, ↓ HDL), hypothyroidism (↑ LDL, ↑ TG), nephrotic syndrome (↑ LDL, ↑ TG), liver failure (↓ LDL), alcohol (↑ TG, ↑ HDL), thiazides (↑ LDL, ↑ TG), protease inhib (↑ TG)

Drug Treatment			
Drug	**↓ LDL**	**↓ TG**	**Side Effects/Comments**
Statins	30–60%	10–25%	↑ ALT in 0.5–3%; ✓ before starting and then prn. Myalgias <10%, rhabdo <0.1%, dose-dependent ↑ risk of DM (*Lancet D&E* 2024;12:306).
Ezetimibe	~24%	—	Well tolerated
Bempedoic acid	~18%	—	Hyperuricemia/gout
PCSK9i	50–60%	15–25%	mAb inj SC q2–4w or siRNA inj SC q6mo
Fibrates	5–15%	35–50%	Myopathy risk ↑ w/ statin. ↑ Cr; ✓ renal fxn q6mo.
Ω-3 FA	5% ↑	25–50%	EPA & DHA at doses of up to 4 g/d No benefit to low-dose supplementation

Resins ↓ LDL-C by ~20%, but not well tolerated; niacin ↑ HDL-C and ↓ TG & LDL-C, but no effect on CV outcomes

Treatment of LDL-C (*JACC* 2022;801:1366)

- **Statins:** every 1 mmol (39 mg/dL) ↓ LDL-C → 22% ↓ major vascular events (CV death, MI, stroke, revasc) in individuals w/ & w/o CAD (*Lancet* 2016;388:2532)
- **Ezetimibe:** ↓ MACE as monoRx & when added to statin (*NEJM* 2015;372:2387; *Lancet* 2022;400:380)
- **PCSK9 inhibitors:** ↓ MACE (*NEJM* 2017;376:1713 & 2018;379:2097)
- **Bempedoic acid:** ↓ MACE in statin-intolerant Pts (*NEJM* 2023;388:1353)
- In homozygous FH: apheresis; evinacumab (ANGPTL3 inhib) ↓ LDL-C by ~50%

Treatment of other lipids (*Lancet* 2014;384:618 & 626)

- **HDL-C:** low levels a/w ↑ risk of MI, but no clinical benefit shown by raising
- **Triglycerides:** reasonable to treat levels >500 mg/dL w/ fibrates or Ω-3 FA to ↓ risk of pancreatitis. May be a/w CAD (*NEJM* 2014;371:22). 4 g/d of EPA ↓ CV risk, but 2 g/d EPA + 2 g/d DHA did not despite similar ↓ TG (*NEJM* 2019;380:11; *JAMA* 2020;324:2268). APOC3 inhibitors being developed (*NEJM* 2024;390:1781 & 392:127).
- **Lp(a):** PCSK9i ↓ ~25%. siRNA that ↓ ≥90% under study (*NEJM* 2022;387:1855).

2018 ACC/AHA Chol. Guidelines & 2022 ECDP (*Circ* 2019;139:e1082; *JACC* 2022;80:1366)	
Population	**Recommendation**
Very high-risk ASCVD*	High-intensity statin; add EZE or PCSK9i if LDL-C ≥55
Clinical ASCVD	High-intensity statin, add EZE or PCSK9i if LDL-C ≥70
LDL-C ≥190 mg/dL	High-intensity statin; add EZE or PCKS9i if LDL-C ≥100
DM, age 40–75 y	High-intensity statin (? moderate if no CV RFs); add EZE if 10-y risk ≥20% & LDL-C ≥70

Age 40–75 y (and none of above); *calc 10-y risk*	≥20%	High-intensity statin; ? add EZE if LDL-C ≥70
	7.5%–<20%	Moderate-intensity statin; if uncertain consider CAC
	5–<7.5%	Moderate-intensity statin reasonable
	<5%	Emphasize lifestyle

ASCVD incl h/o ACS, stable angina, art. revasc, stroke, TIA, PAD. *Multiple major ASCVD events (MI, stroke, sx PAD) or 1 major event + multiple high-risk conditions (age ≥65, DM, HTN, CKD, smoking, FH, prior PCI/CABG). 10-y CV Risk Score: https://tools.acc.org/ascvd-risk-estimator-plus. Additional risk factors to consider: LDL-C ≥160 mg/dL, met. synd., CKD, FHx premature ASCVD, hsCRP ≥2 mg/L, Lp(a) ≥50 mg/dL, ABI <0.9, high-risk ethnic groups.

Statin Doses & LDL-C Reduction (doubling of dose → 6% further ↓ LDL-C)

Intensity	↓ LDL-C	Rosuva	Atorva	Simva	Prava	Lova	Fluva	Pitava
High	≥50%	20–40	40–80	(80)				
Mod	30–50%	5–10	10–20	20–40	40–80	40	80	2–4

OBESITY AND WEIGHT MANAGEMENT

Epidemiology and assessment (*Lancet* 2024;403:1027)

- Obesity (BMI ≥30) is a chronic disease of excess or abnl adiposity; BMI 25–30 is overweight
- Prevalence of BMI >25: 41% worldwide (predicted >50% by 2035) and >70% in U.S.
- Associated w/ many comorbidities (DM, MAFLD, HTN, OSA), and higher risk of certain malignancies and overall excess mortality
- Body mass index (BMI; kg/m^2) is most common screening test; alternative anthropometrics that capture abd adiposity (eg, waist circumference) may improve risk stratification

Clinical evaluation

- Screen for underlying causes & contributing factors based on history and examination:
  Weight gain promoting meds: some psych, anticonvulsants, insulin, SU, corticosteroids
  Endocrine disorders: eg, hypercortisolism, hypothyroidism, & PCOS
  Psychiatric disorders: depression, eating disorders (eg, binge-eating disorder)
- Identify weight-related complications: eg, HTN, dyslipidemia, T2D, CKD, OSA

Lifestyle and behavioral interventions (*Endocrine Pract* 2016;22(suppl 2):1)

- Dietary goal(s): achieve ~500–750 kcal/d deficit; consider nutritionist referral
- ≥150 min/wk of ≥mod-intensity exercise (≥200–300 min/wk freq. needed to maintain wt ↓)
- Behavioral: self-monitoring of diet & wt, goal-setting, stimulus control, stress reduction

Pharmacotherapy (*JAMA* 2023;330:2000)

- Indications: BMI ≥30 or ≥27-<30 + ≥1 weight-related complication; should be implemented alongside lifestyle modifications
- **Incretin-based**
  GLP-1RA (liraglutide, semaglutide) & dual GLP-1/GIP RA (eg, tirzepatide). Also under study: dual GLP-1 & glucagon agonists; triple agonists; GLP-1RA + GIP antagonist.
  Wt loss is multifactorial: favorable modulation of dysregulated neurometabolic & entero-

endocrine pathways centrally & peripherally (eg, ↓ GI motility) leads to ↑ satiety, ↓ PO intake, and improved insulin sensitivity; CV benefits observed irrespective of DM status
  - Currently approved agents: 12–20% wt loss; also favorable effects on Hb_{A1C} (↓ ~2% in DM), SBP (↓ ~5 mmHg), TG (↓ ~20% mmHg), hsCRP (↓ ~35%) (*NEJM* 2021;385:503)
  - In Pts w/ CVD w/o DM: 20% ↓ MACE & 18% ↓ HF events (SELECT, *NEJM* 2023;389:2221)
  - In Pts w/ DM & PAD (3/4 overwt or obese): ↑ walking distance (*Lancet* 2025;405:1580)
  - In Pts w/ HFpEF: 38% ↓ CV death or worsening HF (SUMMIT, *NEJM* 2025;392:427)
  - In Pts w/ T2D & CKD: 24% ↓ MACE & CKD death (FLOW, *NEJM* 2024;391:109)
  - In Pts w/ MASH & mod fibrosis: ↓ MASH (SYNERGY NASH, *NEJM* 2024;391:299)
  - *Side effects*: nausea, emesis, constipation, abd bloating/cramping; typically mild & during initiation or dose-escalation. Mitigate w/ ↓ meal size & dose-titration protocols.
  - *Contraindic*: pregnancy; personal/FHx medullary thyroid cancer or MEN2a syndrome; hx pancreatitis
  - *Pre-op/anesth recs*: Hold for 7 days pre-op if on weekly, 24-hr if on daily due to aspiration risk in setting of slowed gut motility
- **Non-incretin-based therapies**
  - Can be useful adjuncts, but min wt loss (<5% s/p 12–16 wk) & not shown to impact clinical outcomes
  - Orlistat: pancreatic lipase inhibitor → ↓ TG hydrolysis & FFA absorption; side effects: steatorrhea
  - Naltrexone–bupropion: improves central regulation of eating behaviors; side effects: nausea & HA; avoid in pregnancy, uncontrolled HTN, seizure disorder, chronic opioid use
  - Phentermine–topiramate: ↓ appetite centrally; side effects: dry mouth, paresthesias, insomnia; avoid in preg, established CVD, glaucoma, untreated hyperthyroidism

Metabolic surgery (*Obes Surg* 2023;33:3)

- Indications: BMI ≥35 or 30–<35 + metabolic disorder (eg, DM or MASH); for Asian adults, metabolic surgery can be considered at BMI ≥27.5 if other indications
- Expected wt reduction at 1 yr: ~25% w/ laparoscopic sleeve gastrectomy (LSG) and ~35% with Roux-en-Y gastric bypass (RYGB); at 15 years ~20% & ~30% (*NEJM* 2007;357:741)
- LSG/RYGB ↑ rate of control, remission, or prevention of HTN, DM, dyslipidemia, and MASH compared with usual care (*NEJM* 2012;366:1567 & 2014;370:2002; *Lancet* 2023;401:1786)
- Risk of perioperative mortality low (~0.2%); other complications include anastomotic leak/stricture, marginal ulceration/internal hernia (RYGB: 2–5%), micronutrient (eg, iron) deficiencies, and recurrent weight gain (~20–40% w/ regain of ≥25% lost weight long-term); increased risk of bone loss and fractures

NOTES

APPROACH TO RHEUMATIC DISEASE

Major categories of inflammatory rheumatic disease

- **Inflammatory arthritis**: crystalline (gout, CPPD), RA, spondyloarthritis, adult-onset Still's
- **Connective tissue disease**: SLE, Sjögren's, scleroderma, myositis (DM, PM), MCTD
- **Vasculitis**: large (GCA, Takayasu's); medium (PAN); small (ANCA, IgA, cryo); Behçet's
- **Others**: IgG4-related disease, autoinflammatory disease (familial Mediterranean fever, TNF receptor–associated periodic syndrome, VEXAS = vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic), sarcoid (see "ILD"), HLH/MAS, relapsing polychondritis

Approach to patient with joint pain

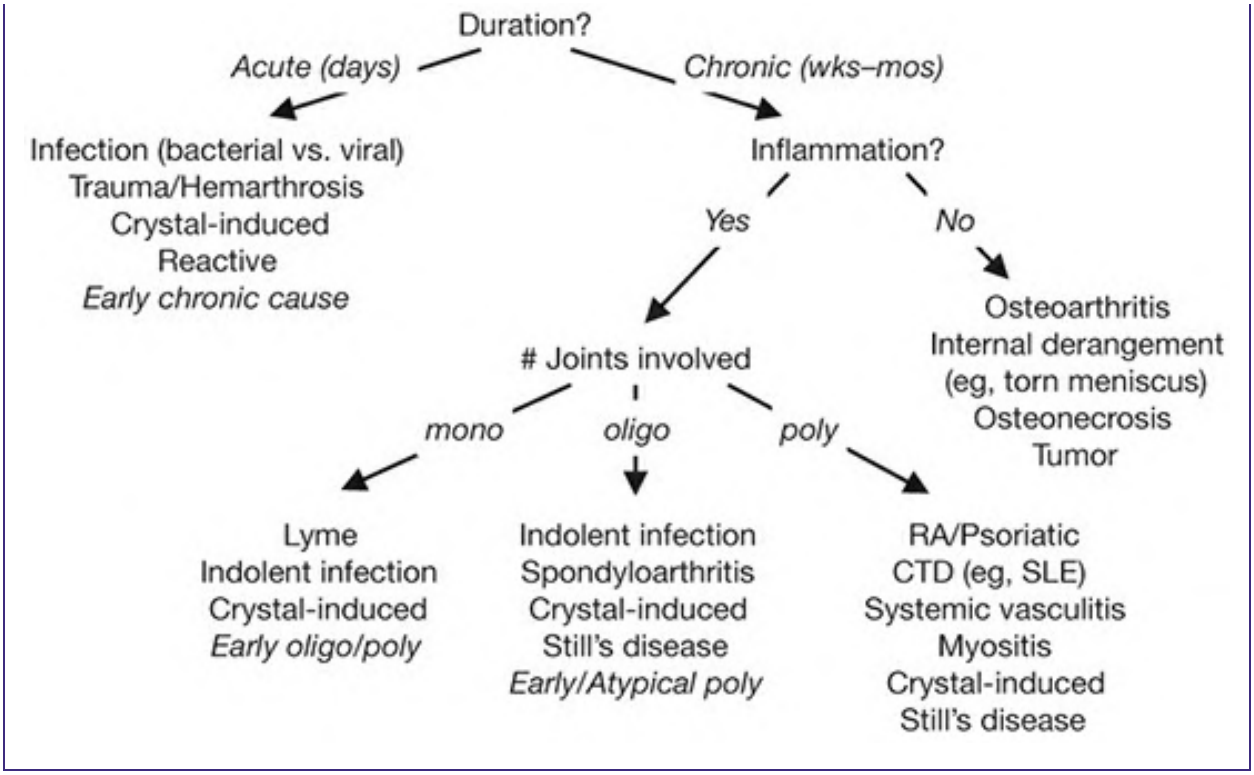
- **Articular** vs. **periarticular** (bursitis, tendinitis, enthesitis) source of pain: typically active ROM more painful than passive ROM in periarticular process
- **Inflammatory** vs. **noninflammatory** pain: *features of inflammatory arthropathy* include joint swelling, warmth or redness, prolonged morning stiffness (>30 min), improvement of pain/stiffness w/ motion/exercise. Assess for extra-articular features.
- Physical exam: identify signs of inflammation, number and pattern of affected joints

Key Physical Exam Findings in Joint Pain

	Articular (Joint) Disease			*Periarticular/Soft Tissue*	
Physical Exam	**OA**	**Inflammatory Arthritis[a]**	**Arthralgia**	**Bursitis or Tendinitis**	**Myofascial**
Swelling	Varies	Yes	No	Yes	No
Erythema	No	Varies	No	Yes	No
Warmth	No	Yes	No	Yes	No
Tenderness	Joint line	Yes	Varies	Periarticular	Yes
ROM[b]	Limited	Limited	Full or limited	Full, often limited by pain	Full
Pain w/ active or passive	Both	Both	Usually both	Active > passive	Usually both

[a]May initially present as arthralgia w/o overt arthritis. [b]Range of motion of joint or joint a/w bursa or tendon.

Figure 8-1 Approach to arthritis



Analysis of Joint Fluid				
Test	**Normal**	**Noninflamm**	**Inflammatory**	**Septic**
Appearance	Clear	Clear, yellow	Clear to opaque yellow-white	Opaque
WBC/mm^3	<200	<2000	>2000	>2000 *(usually >50k*)*
Polys	<25%	<25%	≥50%	≥75%
Culture	⊖	⊖	⊖	⊕
Intracellular crystals	⊖	⊖	⊕ in some (eg, gout)	May be ⊖ or ⊕ if concurrent gout/CPPD

*WBC count of aspirated fluid in septic bursitis often < WBC count in septic arthritis

Imaging features of major arthritides

- **OA:** X-ray: asymmetric joint space narrowing (JSN), **osteophytes**, subchondral sclerosis & cysts; subchondral "gull-wing" erosions may be seen in less-common erosive OA
- **Gout:** X-ray: early = nonspecific swelling; late = **tophus**, joint erosions w/ overhanging edges; U/S: erosions, microtophi (double-contour sign); dual-energy CT (DECT): articular and/or periarticular UrA deposits
- **CPPD:** X-ray: hook-like osteophytes, chondrocalcinosis (knee, wrist). CT: crowned dens.
- **RA:** X-ray: symmetric JSN; early = periarticular **osteopenia;** late = marginal **erosions**; subluxations; MRI & U/S can detect early and subclinical disease; MRI ≈ U/S for erosions
- **Spondyloarthritis:** e/o **sacroiliitis**: X-ray: early = pseudo-widening SI joint space; late = sclerosis, erosions, **ankylosis**; SI MRI ↑ Se for early Δ; U/S ≈ MRI to detect enthesitis

Comparison of Major Arthritides				
Feature	**Primary OA**	**RA**	**Gout/CPPD**	**Spondyloarthritis**
Onset	Gradual	Gradual	Acute	Variable
Inflamm.	⊖	⊕	⊕	⊕
Pathology	Degeneration	Pannus	Crystals, tophi	Enthesitis, arthritis
# of joints	Poly	Poly	Mono to poly	Oligo or poly
Typical joints	Hips, knees, spine, 1st CMC, DIP, PIP	MCP, PIP, wrists, feet, ankles, knees	Gout: foot/ankle CPPD: knee, wrist	Sacroiliac, spine, large peripheral joints
Joints often *spared*	MCP, shoulder, elbow, wrist	L & T spine, DIPs	Spine (spared in gout)	*Any joint can be involved*
Special articular findings	Bouchard's & Heberden's nodes	Ulnar dev., swan neck & boutonnière deformities	Monosodium urate/CPPD crystals; tophi	Dactylitis, enthesitis (eg, Achilles), bamboo spine, syndesmophytes
Extra-articular	None	SC nodules, pulm sx, sicca	Olec. bursitis, renal stones	Psoriasis, IBD, uveitis, urethritis, conjunctivitis
Lab data	Normal	Often ⊕ RF & anti-CCP	↑ UrA (may be nl during flare)	± HLA-B27

Lancet 2025;405:71; 2024;402:2019; 2021;397:1843; *JAMA* 2025;333:408

Inflammatory Marker & Autoantibody Testing

Inflammatory markers (*Mod Rheumatol* 2009;19:469; *NEJM* 1999;340:448)

- **ESR:** *indirect* measure of inflammation [↑ RBC aggregation due to acute-phase proteins (fibrinogen, Ig)]; slow to rise; may ↑ w/ age, preg., anemia, obesity, ESRD. Ddx for >100: malig. esp. MM, lymphoma; GCA or other vasculitis; endocarditis, TB, osteomyelitis.
- **CRP:** *direct* measure of inflammation (protein produced by liver, part of innate immune system); *typically rises and falls before the ESR* w/ treatment/resolution of process

Autoantibody testing (*Best Pract Res Clin Rheumatol* 2014;28:907)

- ANA (antinuclear Ab): *screening test* for Ab directed against nuclear proteins
- Order ANA only when *clinical suspicion for CTD* b/c nonspecific: 1:40 (very low ⊕, 25–30% of healthy Pts); 1:80 (low ⊕, 10–15% of healthy Pts); ≥1:160 (⊕, 5% of healthy Pts). May be ⊕ in Pts prior to clin manifest (*NEJM* 2003;349:1526; *Arthritis Res Ther* 2011;13:1).
- If ANA ⊕ and high clinical suspicion for CTD, consider testing for Ab against dsDNA, Smith, Ro/La, RNP, Scl-70, and myositis-specific Abs (*highly specific* for various CTD)
- ANA does *not* correlate well w/ disease activity, ∴ no clinical value in serial testing
- ANA also ⊕ in: AIH, PBC, thyroid disease, certain infxns and malignancies, IBD, IPF
- RF and anti-CCP (see "Rheumatoid Arthritis"). ANCA (see "Vasculitis").

Ddx & Approach to Common Inpatient Rheum Presentations

Feature	Rheum Ddx	Rheum Lab w/up (+ ANA)

FUO	Vasculitis (GCA, TAK, PAN, ANCA, HSP, cryo), AOSD, SLE, inflam. arthritis, VEXAS	ESR, CRP, ANCA, RF, CCP, ± cryo; arthrocentesis
Pulm HTN	Scleroderma (limited > diffuse), MCTD	centromere, Scl-70, RNA Pol III, RNP
DAH	ANCA vasculitis, Goodpasture's, SLE, APS	ANCA, GBM, C3/C4, APLA
ILD	Scleroderma (diffuse > limited), sarcoid, RA, myositis (DM, antisynthetase, MDA5), Sjögren's (often cystic = lymphoid interstitial PNA), MCTD, ANCA vasculitis (esp. MPA)	Scl-70, RF/CCP, CK, aldolase, ± myositis-specific Abs, Jo-1, Ro/La, ANCA
Pleuro-pericarditis	SLE, RA, MCTD, scleroderma, myositis > ANCA vasculitis, Sjögren's, AOSD, PAN	dsDNA, RF/CCP, Sm, RNP, Ro/La, Scl-70, ANCA
AKI + active sed. or CTD s/s	SLE (GN or nephrotic), ANCA vasculitis (GN), scleroderma renal crisis, Sjögren's (RTA/TIN), PAN (infarct), HSP, Goodpasture's, cryo, APS	dsDNA, Sm, RNP, Ro/La, C3/C4, Scl-70, RNA Pol III, ANCA, GBM, cryos, APLA
Neuropathy	ANCA vasculitis, Sjögren's, cryo, sarcoid, RA, PAN, SLE	Ro/La, ANCA, cryo RF/CCP, HCV, HBV

INFECTIOUS ARTHRITIS & BURSITIS

Etiologies & Diagnosis of Infectious Arthritis

Etiologies (*Am Fam Physician* 2021;104:589)

- **Bacterial** (nongonococcal): early diagnosis and treatment essential
- **Gonococcal** (*N. gonorrhoeae*): consider in sexually active young adults
- Viral: parvovirus, HCV, HBV, acute HIV, Chikungunya; mainly polyarticular, may mimic RA
- Mycobacterial: monoarticular or axial (Pott's disease)
- Fungal: *Candida* (esp. prosthetic joints), coccidioidomycosis (valley fever), histoplasmosis
- Other: Lyme (qv), *Mycoplasma*, *Salmonella*, Brucellosis, *T. whipplei*

Diagnosis (*JAMA* 2007;297:1478)

- H&P w/ poor sensitivity and specificity for septic arthritis
- **Arthrocentesis in acute-onset inflammatory monoarthritis** to r/o septic arthritis; if possible, obtain fluid sample prior to starting antibiotics
- Do not tap through overlying infected area to prevent introducing infxn into joint space
- ✓ Fluid cell count w/ diff, Gram stain, bacterial culture, crystal analysis; **WBC >50k w/ PMN predominance** suspicious for bact. infxn; *crystals do not r/o septic arthritis!*

Bacterial (Nongonococcal) Arthritis

Epidemiology & risk factors (*Infect Dis Clin North Am* 2017;31:203)

- 1/50,000 incidence per year
- **Immunocompromised host:** DM, EtOH use, HIV, age >80, SLE, cancer, steroid use, etc.
- **Damaged joints:** RA, OA, gout, trauma, prior surgery/prosthetic, prior arthrocentesis (rare)
- **Bacterial seeding:** bacteremia especially secondary to IVDU or endocarditis; direct inoculation or spread from contiguous focus (eg, cellulitis, septic bursitis, osteomyelitis)

Clinical manifestations (*JAMA* 2007;297:1478; *Lancet* 2010;375:846)

- Acute-onset **monoarticular arthritis** (>80%) w/ pain (Se 85%), swelling (Se 78%), warmth
- Location: **knee** (most common), hip, wrist, shoulder, ankle. In IVDU, tends to involve other areas including axial joints (eg, SI, symphysis pubis, sternoclavicular, manubrial joints).
- **Constit. sx:** fevers (Se 57%), rigors (Se 19%), sweats (Se 27%), malaise, myalgias
- Infection can track from initial site to form fistulae, abscesses, or osteomyelitis
- *Septic bursitis must be differentiated from septic arthritis (intra-articular infection)*

Additional diagnostic studies (*JAMA* 2007;297:1478)

- **Synovial fluid: WBC usually >50k** (Se 62%, Sp 92%) but can be <10k, >**90% polys;** Gram stain ⊕ in ~75% of *Staph*, ~50% of GNR; Cx ⊕ in >90%; synovial bx most sens.
- **Leukocytosis** (Se 90%, Sp 36%); **elevated ESR/CRP** (Se >90%)
- **Blood cultures** ⊕ in >50% of cases, ~80% when more than 1 joint involved
- X-rays of joints should be obtained, but usually normal until after ~2 wk of infection when may see bony erosions, joint space narrowing, osteomyelitis, and periostitis
- **CT & MRI** useful esp. for suspected hip infection or epidural abscess

Treatment for native joints (*IDCNA* 2017;31:203)

- Ortho consult. Prompt empiric antibiotics guided by Gram stain after surgical drainage/washout. If Gram stain ⊖, empiric Rx w/ staph coverage; add anti-pseudomonal agent if IVDU or immunocompromised.

Common Microbes (by Gram stain)		Population	Initial Antibiotic Regimen (tailor per Gram stain, cx, clin course)
GPC clusters	*S. aureus* (most common)	Normal joints Prosthetic joints Damaged joints	Vancomycin. Can later Δ to antistaphylococcal penicillin or cefazolin based on sensitivities.
	S. epidermidis	Prosthetic joints Postprocedure	
GPC chains	Streptococci	Healthy adults Splenic dysfunction	PCN-G or ampicillin
GN	Diplococci: *N. gonorrhoeae*	Sexually active young adults	3rd-gen cephalosporin (ceftriaxone, cefotaxime)
	Rods: *E. coli, Pseudomonas, Serratia*	IVDU, GI infection immunosupp, trauma elderly	3rd-gen cephalosporin. Pseudomonal coverage if risk factors.

- **IV antibiotics** × ≥2 wk followed by oral antibiotics; varies by clinical course & microbiology
- Often requires serial drainage w/ arthroscopy or arthrocentesis. Expect ↓ WBC and sterility.
- 10–15% mortality (up to 50% w/ polyarticular); depends on virulence, time to Rx, host

Prosthetic joint infections (*NEJM* 2023;388:251)

- ↑ risk in first 2 y s/p procedure; rate generally low (0.5–2.4%); risk factors include obesity, RA, immunocompromised state, steroids, & superficial surgical site infxn
- Staphylococci (coag negative & *S. aureus*) in >50%; polymicrobial in 10–20%
- Early (<3 mo s/p surgery) or delayed (3–24 mo) onset of sx from microbe typically acquired during implantation; early w/ virulent (eg, MRSA) and delayed w/ less virulent organisms (eg, *P. acnes*, coag negative *Staph*) & more indolent presentation
- Late (>24 mo) onset typically related to secondary hematogenous seeding

- Diagnosis requires arthrocentesis; ESR & CRP (CRP Se 73–91%, Sp 81–86%; *NEJM* 2009;361:787) can be helpful. Loosening hardware on imaging can be clue.
- Requires prolonged abx (initial empiric regimen: vanc + 3rd/4th-gen cephalosporin) (*NEJM* 2021;384:1991) & hardware replacement (retention a/w ~40% failure; *CID* 2013;56:182) or lifelong suppressive abx. *Consult ID & orthopedics*.

Disseminated Gonococcal Infection (DGI)

Epidemiology (*Infect Dis Clin North Am* 2005;19:853)

- *N. gonorrhoeae*; most frequent type of infectious arthritis in sexually active young adults
- **Normal host** as well as Pts w/ deficiencies of terminal components of complement
- ♀:♂ = 4:1 historically, but now ↑ in ♂. Occurs in <3% of *N. gonorrhoeae* infxn; ↑ incidence w/ menses, pregnancy, postpartum, SLE; ↑ incidence in MSM.

Clinical manifestations (*Best Pract Res Clin Rheumatol* 2003;17:201)

- Preceded by **mucosal infection** (eg, cervix, urethra, anus, or pharynx) that is often asx
- Two distinct syndromes, although Pts can have both:
  Joint-localized: purulent arthritis (40%), usually 1–2 joints (knees > wrists > ankles)
  Arthritis-dermatitis syndrome: triad of **polyarthralgias, tenosynovitis, skin lesions**
  1. *polyarthralgias*: migratory joint pain, can affect small or large joints
  2. *tenosynovitis*: pain/inflammation of tendon and its sheath in wrists, fingers, ankles, toes
  3. *skin lesions*: gunmetal gray pustules with erythematous base on extremities & trunk
- Rare complications: Fitz–Hugh–Curtis syndrome (perihepatitis), pericarditis, meningitis, myocarditis, osteomyelitis from direct extension of joint-localized infection

Additional diagnostic studies

- Synovial fluid: **WBC** >**50k** (but can be <10k), **poly predominant**
  Gram stain ⊕ in ~25%; culture ⊕ in up to 50% if done w/ Thayer–Martin media
- BCx: more likely ⊕ in arthritis-dermatitis syndrome; rarely in joint-localized disease
- Gram stain and culture of skin lesions occasionally ⊕
- Cervical, urethral, pharyngeal, rectal PCR or cx on Thayer–Martin media; ✓ *Chlamydia*

Treatment

- **Ceftriaxone** × **7–14 d w/ empiric doxycycline** × **7 d** for *Chlamydia* if coinfection has not been excluded (see STI)
- Joint arthroscopy/lavage may be required for purulent arthritis; rarely >1 time

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Olecranon & Prepatellar Bursitis

Epidemiology & risk factors (*Joint Bone Spine* 2019;86:583)

- >150 bursae in the body; 2 most commonly infected are **olecranon** and **prepatellar**
- Most commonly (esp. superficial bursae) due to direct trauma, percutaneous inoculation, or contiguous spread from adjacent infection (eg, cellulitis)
- Other risk factors: recurrent noninfectious inflammation (eg, gout, RA), diabetes
- *S. aureus* (80%) most common, followed by streptococci

Diagnosis

- Physical exam: discrete bursal swelling, erythema, maximal tenderness at center of bursa with preserved joint range of motion

- Aspirate bursa if concern for infxn, ✓ cell count, Gram stain, bacterial cx, crystals
  WBC >**20k w/ poly predominance** suspicious for bacterial infection, but lower counts very common (crystals do *not* rule out septic bursitis!)
- Assess for adjacent joint effusion, which can also be septic
- Do *not* tap through infected skin to avoid introducing infxn into bursa

Initial therapy

- Prompt empiric coverage for staphylococci and streptococci: PO abx acceptable for mild presentation; **vancomycin** if ill appearing; broaden spectrum based on risk factors
- Modify antibiotics based on Gram stain, culture results, & clinical course. Duration of Rx is 1–3 wks. **Serial aspirations** every 1–3 d until sterile or no reaccumulation of fluid.
- Surgery if unable to drain bursa through aspiration, evidence of foreign body or necrosis, or recurrent/refractory bursitis w/ concern for infxn of adjacent structures

CRYSTAL DEPOSITION ARTHRITIDES

Comparison of Gout and Pseudogout

	Gout (*Rheumatology* 2018;58:27)	**Pseudogout** (*NEJM* 2016;374:2575)
Acute clinical	Sudden onset painful *monoarticular* arthritis (classically **podagra** [great toe MTP]) or bursitis; freq. at night May be *polyarticular* in subseq flares Can mimic cellulitis (esp in foot)	Mono- or asymmetric oligoarthritis (esp knees, wrists, and MCP joints); rare axial involvement (eg, crowned dens syndrome)
Chronic clinical	Solid crystal deposition (**tophus**) in joints (esp. toes, fingers, wrists, knees) & tissue (esp. olecranon bursa, pinna, Achilles)	"Pseudo-RA" w/ polyarticular arthritis w/ morning stiffness or "Pseudo-OA"
Assoc. conditions	Metabolic syndrome; CKD; CHF	**3 H's:** Hyper-PTH, Hypo-Mg, Hemochromatosis
Crystal	Monosodium urate (MSU)	Ca pyrophosphate dihydrate
Polarized microscopy*	Needle-shaped, **negatively birefringent**	Rhomboid-shaped, weakly **positively birefringent**
Radio-graphic findings	Early = nonspecific tissue swelling Late = tophus, joint erosions w/ overhanging edges "Double-contour sign" on MSK US DECT: UrA vs. Ca deposits	**Chondrocalcinosis:** linear densities within articular cartilage; often found in menisci, fibrocartilage of wrist, hands, symphysis pubis
Other	a/w uric acid stones; urate nephropathy	✓ Ca, Mg, iron studies, UrA, PTH in young or severe cases

*Intracellular crystals more specific. Infection can coexist with acute attacks. ∴ always ✓ Gram stain & Cx.

GOUT

Definition & epidemiology (*Lancet* 2021;397:1843; *JAMA Netw Open* 2023;6:e239501)

- Humans lack enzyme (uricase) to metabolize urate (end-product of purine metabolism)
- MSU crystals activate inflammasome, promoting joint/periarticular inflammation

- Prev >1/20 American adults, ♂ > ♀; peak incidence ↑ with age; most common inflamm arthritis in ♂ over 30 y; *rare* in premenopausal ♀ (estrogens ↑ renal urate excretion)
- Apparent bidirectional cardiometabolic/renal comorbidity risk (*Nature Rev Rheumatol* 2022;18:97)

Etiologies

- UrA underexcretion (85–90%): meds (eg, diuretics, ASA), ↓ GFR, obesity
- Uric acid (UrA) overproduction (10–15%): ↑ calories, meat, seafood, EtOH, fructose, psoriasis, myelo- and lymphoproliferative disease, chronic hemolytic anemia, cytotoxic drugs, rare inherited enzyme defic, genetic variants (*Nature Rev Rheumatol* 2018;14:341)

Diagnosis (*Rheumatology* 2023;62:1493)

- ↑ **UrA is not diagnostic;** 25% of measurements nl during flare; ± ↑ WBC & ESR
- Targeted ultrasound may have high dx accuracy
- **Arthrocentesis is gold standard:** intracellular negatively birefringent needle-shaped MSU crystal. U/S w/ double-contour sign or dual-energy CT (DECT) can aid dx.

Acute treatment (*Arthritis Care Res* 2020;72:744; *NEJM* 2022;387:1877)

- Colchicine, NSAIDs, & steroids all 1st-line; choice guided by side-effect profile/comorbidities. IL-1R inhibitor or ACTH if these contraindicated. Start Rx ASAP; continue until acute flare resolves; consider combo Rx if severe; rest/ice; self-limited w/in 3–21+ d w/o Rx.
- Continue urate-lowering therapy during attack if already taking

Acute Treatment for Gout

Drug	Initial Dose	Comments
NSAIDs (nonsel or COX-2 inhib)	Full anti-inflammatory dose → tapering	Gastritis & GIB risk. Avoid in CKD & CVD. ≈ efficacy among NSAIDs.
Colchicine	1.2 mg → 0.6 mg 1 h later → 0.6 mg bid. Early Rx most effective.	N/V/diarrhea (w/ ↑ dose), marrow suppression, myopathy, neuropathy. ↓ dose in CKD.
Corticosteroids (PO, IA, IV, IM)	eg, prednisone 0.5 mg/kg/d × 5–10 d ± taper	Rule out joint infection first. Intraarticular injection if mono/oligoarticular.
IL-1R/IL-1β inhibitors	anakinra (100 mg SC qd); canakinumab (150 mg SC q3m)	↑↑ cost (*Ann Rheum Dis* 2012;71:1839; *Arthritis Rheumatol* 2021;73:1533)
ACTH (IM)	eg, 100 IU IM ×1–2 doses	↑ cost, ↓ s/e, limited data (*Semin Arthritis Rheum* 2014;43:648)

Chronic treatment (*Arth Care Res* 2020;72:744; *Curr Opin Rheum* 2021;33:135; *NEJM* 2022;387:1877)

- **Approach:** if ≥2 attacks/y, tophus, joint erosions → start urate-lowering therapy + pharm. ppx to ↓ risk of acute attack. Consider if 1st flare + CKD ≥3 or urolithiasis.
- **Urate-lowering therapy (ULT):** goal UrA <6 mg/dL; when starting ULT, always give with pharm Ppx as below; *do NOT d/c during acute attack or due to AKI*
- **Pharmacologic prophylaxis:** continue 3–6 mo w/ above Rx or longer if continued attacks
  Low-dose **colchicine** (~50% ↓ risk of acute flare; *J Rheum* 2004;31:2429), **NSAIDs** (less evid.; *Ann Rheum Dis* 2006;65:1312), low-dose **steroids**, **IL-1/1R inhibitors** (vide supra)
- **Lifestyle** Δs: ↓ red & organ meats, EtOH, some seafood; ↑ wt loss; Mediterranean/DASH diet; avoid dehydration

Urate-Lowering Therapy (Chronic Treatment for Gout)		
Drug (route)	**Mechanism**	**Comments**
Allopurinol (PO)	Xanthine oxidase inhibitor	1st line; ↓ starting dose in CKD; titrate ↑ q2–5wk (dose can be >300 mg/d even in CKD). Max = 800 mg/d. A/w rash, hypersensitivity syndrome (vide infra), BM suppression **(avoid w/ AZA/6-MP)**, diarrhea, N/V, hepatitis; monitor CBC, LFTs; *not nephrotoxic.*
Febuxostat (PO)	Nonpurine xanthine oxidase inhib	2nd line; use if allopurinol intolerant; a/w ↑ LFT, rash, arthralgias, N/V; **avoid w/ AZA/6-MP** (BM suppression); start 40 mg, max dose = 120 mg/d
Pegloticase (IV)	Recombinant uricase	For refractory tophaceous gout; infusion reactions (including anaphylaxis); Ab formation may limit use (*JAMA* 2011;306:711); **avoid w/ G6PD deficiency**
Probenecid (PO)	Uricosuric	Rarely used; risk of urolithiasis

- **Allopurinol hypersensitivity syndrome:** 10–25% mortality; incidence ~5/1000. ↓ risk w/ *starting* dose 100 mg/d if eGFR >40 (50 mg/d if eGFR ≤40). Titrate by 100 mg/d (eGFR >40) or 50 mg/d (eGFR ≤40) q2–5wk until UrA <6 mg/dL. *A/w HLA-B5801*, esp. Han Chinese, Koreans, Thai, African Americans; screen in these high-risk groups prior to start.

Calcium Pyrophosphate Dihydrate (CPPD) Deposition Disease/Pseudogout

Definition (*NEJM* 2016;374:2575)

- Deposition of CPPD crystals within tendons, ligaments, articular capsules, synovium, cartilage; frequently asymptomatic

Etiologies (*Nat Rev Rheumatol* 2018;14:592)

- Most cases ***idiopathic*;** consider further metabolic eval in young (<50 y) and florid forms
- Metabolic (*3 H's*): hemochromatosis; hyperparathyroidism; hypomagnesemia (esp. in Gitelman's or Bartter's syndromes)
- Joint trauma (incl. previous surgery); intra-articular hyaluronate may precipitate attacks
- Familial chondrocalcinosis (autosomal dominant disorder); early-onset, polyarticular

Clinical manifestations (*Lancet Rheumatol* 2024;6:e791)

- **Chondrocalcinosis:** calcification of cartilage, resulting from CPPD crystal deposition in articular cartilage, fibrocartilage, or menisci
  - ↑ incidence w/ age; can be asymptomatic; chondrocalcinosis in 20% >60 y at autopsy
- **Acute crystal arthritis (pseudogout):** CPPD crystal-induced mono- or asymmetric oligoarthritis, *indistinguishable from gout except via crystal analysis or DECT*
  - location: **knees**, **wrists**, MCPs; rarely, axial (crowned dens syndrome = CPPD at C1–C2)
  - precipitants: surgery, trauma, or severe illness
- Chronic forms: "pseudo-RA" (symmetric polyarthritis of MCPs, wrists) and "pseudo-OA" (resembles OA with enhanced structural damage)

Diagnostic studies

- Arthrocentesis is gold standard: **rhomboid-shaped, weakly *positively* birefringent crystals**

(yellow *perpendicular &* blue *parallel* to axis on polarizer; see table above)
- Radiographs: see table above

Treatment (*NEJM* 2016;374:2575)

- Asymptomatic chondrocalcinosis requires no treatment
- Acute therapy for pseudogout: extrapolated from practice in gout. Limited RCTs suggest equivalent efficacy of colchicine or anakinra vs. prednisone (*Lancet* 2023;4:E523; *Joint Bone Spine* 2021;88:105088).
- If associated metabolic disease, Rx of underlying disorder *may* improve arthritis sx
- Low-dose daily colchicine may be effective for prophylaxis or chronic arthropathy. Data less clear for MTX, HCQ, or anakinra for chronic arthropathy (*Lancet Rheumatol* 2024;6:e791).

RHEUMATOID ARTHRITIS (RA)

Definition & epidemiology (*NEJM* 2023;388:529; *Lancet* 2024;402:2019)

- Chronic, symmetric, and potentially destructive inflammatory polyarthritis characterized by proliferative synovial tissue (pannus) formation in affected joints
- Complex pathogenesis likely initiated by mucosal (lung, GI, periodontal) inflammation that drives autoantibody production and activates multiple immune and synovial cell types
- Risk factors include genetics (~50% of risk; HLA-DRB1 “shared epitope”), exposures (smoking, silica dust), and Pt factors (periodontal disease, gut microbiome)
- Prevalence = 1/100 adults and 1/20 ♀ >70 y; ♀ to ♂ ratio = 3:1; highest incidence 40–75 y

Clinical manifestations

- Usually insidious onset **pain**, **swelling**, & ↓ function of joints w/ prolonged **morning stiffness** >30 m for ≥6 wk (typically PIPs, MCPs, wrists, knees, ankles, MTPs)
- Polyarticular (60% small joints, 30% large joints, 10% both), but may be monoarticular (knee, shoulder, wrist) early in course. Affected joints more susceptible to infection.
- Joint deformities: **ulnar deviation**, **swan neck** (MCP flexion, PIP hyperextension, DIP flexion), **boutonnière** (PIP flexion, DIP hyperextension), **cock-up deformities** (toes)
- **C1–C2 instability (30%)** → myelopathy; ✓ C-spine flex/ext films before elective intubation
- **Extra-articular manifestations:** can occur at any time; ↑ frequency with seropositivity, smoking, and active disease

Extra-Articular Manifestations	
General	**Fatigue, weight loss**
Skin	**Rheumatoid nodules** (20–30%, usually sero ⊕): extensor surface, bursae; can be in lung, heart, sclera Raynaud’s, pyoderma gangrenosum, Sweet synd., vasculitis (ulcers, purpura)
Pulm	**ILD** (UIP > NSIP pattern; a/w *MUC5B* mutations), airway disease, pleuritis, effusions (low glucose), nodules, pulm HTN; precedes joint sx in 20%
CV	Accelerated athero w/ ↑ **risk of MI & CV death**; pericarditis > myocarditis; coronary/systemic vasculitis (*Nat Rev Rheum* 2020;16:361)
Nervous	Carpal tunnel, stroke, radiculopathy, pachymeningitis, vasculitic lesions
Ocular	Scleritis, episcleritis, keratoconjunctivitis sicca (2° Sjögren’s)

Heme	Anemia of chronic dis., neutropenia (Felty syndrome: triad of sero ⊕ erosive RA, neutropenia, splenomegaly); large granular lymphocyte leukemia, NHL (DLBCL), amyloidosis, ↑ DVT risk
Renal	Glomerulonephritis (usually mesangial), nephrotic syndrome (2° amyloidosis)
Vasculitis	Small & medium vessels (usually ↑ RF titer, long-standing undertreated RA); ulcers, scleritis, & neuropathy most common

Laboratory & radiologic studies

- **RF** (IgM/IgA/IgG anti-IgG Fc) ⊕ in ~70%; nonspecific: seen in other rheumatic diseases (SLE, Sjögren's), cryoglobulinemia, infection (SBE, hepatitis, TB), ~5% of healthy pop.
- **Anti-CCP** (Ab to cyclic citrullinated peptide): ⊕ in ~70%, similar Se but more Sp (>90%) than RF (*Arth Rheum* 2009;61:1472); a/w increased joint damage and lower remission rates
- ~20% seronegative (RF *and* anti-CCP ⊖); ↑ ESR/CRP but nl in ~30%; ⊕ ANA in ~40%
- Radiographs of hands and wrists: periarticular osteopenia, bone erosions, joint subluxation
- Increasing use of MSK U/S to diagnose synovitis, tenosynovitis, and erosive disease

ACR/EULAR classification criteria (*Arth Rheum* 2010;62:2569)

- Used in clinical research, but not for clinical dx
- Likelihood of RA ↑ w/ higher # (espec. ≥4) of small joints, sero ⊕, ↑ ESR/CRP, sx ≥6 wk

Management (*Arth Care Res* 2021;73:924; *Lancet* 2024;402:2019)

- Early dx and Rx w/ frequent follow-up and escalation of Rx as needed with **goal to achieve clinical remission** or low disease activity to avoid irreversible damage
- *Rapid-acting drugs:* limit use to bridge until DMARD takes effect
  - **NSAIDs** or COX-2 inhibitors: ↑ CV, renal, GI risk; consider PPI
  - **glucocorticoids**: low dose (<20 mg/d oral) or joint injection
  - NSAIDs + glucocorticoids: ↑↑ GI events; give PPI and minimize long-term concurrent use
- *DMARDs (disease-modifying antirheumatic drugs):* expect 1–3 mos to take effect
  - **Hydroxychloroquine** consider as monotherapy for mild disease
  - **MTX**: 1st line for mod–severe RA unless contraindic. (CKD, cirrhosis, EtOH, preg)
  - If inadequate response after 3 mo (despite DMARD dose escalation) consider:
    - **combo Rx** w/ other cDMARDs (eg, "triple therapy" w/ MTX, SSZ, and HCQ; *NEJM* 2013;369:307) *or* **adding biologic** (anti-TNF typically 1st line) *or* **JAKi**
    - Concurrent MTX may decrease neutralizing autoantibody formation to biologics
    - JAKi: ↑ infection, cancer, CV, thrombotic risk (*Lancet* 2018;391:2503 & 2513; *NEJM* 2020;383:1511 & 2022;386:316)
- Given a/w CV morbidity/mortality, ↓ risk w/ lifestyle mgmt, lipid & DM screening

RA Therapeutics (*Arthritis & Rheum* 2020;72:529; *Arth Care Res* 2021;73:924)

Class	Drug	Side Effects
Conventional DMARDs (cDMARD)	Hydroxychloroquine (HCQ) Methotrexate (MTX) Leflunomide (LEF) Sulfasalazine (SSZ)	HCQ: retinopathy, rash MTX: stomatitis, pneumonitis MTX and LEF: myelosuppression, GI upset, hepatotoxicity, teratogenic Supplement MTX w/ folate ✓ *G6PD prior to SSZ*
Biologic DMARDs	Anti-TNF: etanercept, infliximab, adalimumab, certolizumab, golimumab CTLA4-Ig: abatacept	↑ risk bacterial/fungal/viral infxn ✓ TB, Hep B/C before starting Immunize (Zoster, pneumococ., etc.) Anti-TNF: ? risk for CHF & CNS

	Anti-IL-6R: tocilizumab, sarilumab Anti-CD20: rituximab (RTX) Recomb. IL-1R antag.: anakinra ***Do not combine biologics***	demyelinating disease Anti-IL-6R: risk of GI perforation Rituximab: infusion rxn, viral reactiv. (PML, HBV [prophylax if + HBcAb])
Targeted synthetic DMARDs	JAKi: tofacitinib, baricitinib; upadacitinib (JAK1 selective) *Do not combine with biologics*	Infxn, ↑ LFTs, VTE, CV events, malignancy, death. Unclear safety in pregnancy.

ADULT-ONSET STILL'S DISEASE (AOSD) & RELAPSING POLYCHONDRITIS

Adult-onset Still's disease (*Lancet Rheumatol* 2025;7:e127; *Rheumatology* 2024;63:1656)

- **Rare autoinflammatory syndrome**, <4/million per y incidence; ♂ = ♀; bimodal onset 15–25 or 36–46 y; sx evolve over wks to mos. Systemic juvenile idiopathic arthritis likely same disease.
- Yamaguchi criteria: requires 5 & ≥2 major; exclude infxn, malig, other rheumatic, drug rxn
  - **Major:** fever ≥39°C for ≥1 wk (usually daily or twice-daily high fever); arthralgias/arthritis ≥2 wk; Still's rash (often intermittent mirroring fever curve); ↑ WBC w/ 80% PMN
  - **Minor:** sore throat; lymphadenopathy; HSM; ↑ AST/ALT/LDH; negative ANA & RF
- Still's rash (>85%): nonpruritic macular or maculopapular salmon-colored rash; usually trunk or extremities; may be precipitated by trauma (Koebner phenomenon), warm water
- Elevated ESR, CRP, ferritin, IL-18
- Plain films: soft tissue swelling (*early*) → cartilage loss, erosions, carpal ankylosis (*late*)
- Rx: NSAIDs (mild disease), steroids, **IL-1** or IL-6 inhibition (**anakinra**/canakinumab or tocilizumab). Consider JAKi if refractory. TNFi or MTX reasonable if mostly arthritis.
- Variable clinical course: long-term remission, remitting–relapsing pattern, or chronic (esp. arthritis); ↑ risk of macrophage activation syndrome (life-threatening)

Relapsing polychondritis (*Nat Rev Rheumatol* 2024;20:347)

- Inflammatory destruction of cartilaginous structures; typical onset age 40–60, ♂=♀, 1/million per y incidence
- Subacute onset of **red**, **painful**, and **swollen cartilage;** ultimately atrophic & deformed
- Multiple sites of cartilaginous inflammation: auricular (pinna) chondritis (*spares lobule*), nonerosive inflammatory arthritis, costochondritis, nasal chondritis, laryngeal or tracheal chondritis, valvulopathy. Scleritis/episcleritis and cochlear/vestibular dysfxn.
- Ddx: VEXAS (esp. if ♂ w hematologic [eg, ↑ MCV], pulm, heart, or ocular involvement), auricular infx (involves lobule), checkpoint inhibitor toxicity, vasculitis (eg, GPA)
- 20–40% a/w autoimmune disease (eg, RA, SLE, Sjögren's, IBD) or hematologic malig
- Labs: ESR, CRP. ✓ UBA1 somatic mutations if concern for VEXAS.
- Bx (not req for dx): proteoglycan depletion, perichondrial inflammation and replacement with granulation tissue and fibrosis; immunofluorescence with Ig and C3 deposits
- Screen for pulm (PFTs, CXR/CT, ± bronch) and cardiac (ECG, TTE) involvement
- Rx guided by disease activity/severity: steroids 1st line; NSAIDs for arthralgias, mild disease; MTX or other DMARD or biologics steroid-sparing; CYC if organ-threatening

SERONEGATIVE SPONDYLOARTHRITIS

Definition and classification system (*NEJM* 2016;374:2563)

- Spondyloarthritis (SpA): group of inflammatory disorders that share common clinical manifestations: inflammation of axial skeleton, peripheral arthritis, enthesitis (vide infra), and extra-articular (primarily ocular, gastrointestinal, and skin disease)
- Seronegative = absence of autoantibodies
- Subtypes: ankylosing spondylitis (AS), psoriatic (PsA), reactive (ReA), IBD-assoc, juvenile SpA, and undifferentiated. *Distinguished by axial vs. peripheral* predominant involvement.

Epidemiology & pathogenesis (*Nat Rev Rheumatol* 2015;11:110)

- Prevalence 1/200 to 1/50 worldwide; AS and non-radiographic axial SpA most common
- HLA-B27 accounts for ~30% of attributable genetic risk but not required for diagnosis
- Environmental factors likely critical for disease, esp reactive arthritis (ie, infection)

Spondyloarthritis (SpA) Epidemiology and Key Presentation Features

Disease	Epidemiology	Key Features
Ankylosing spondylitis (AS)	♂:♀ = 3:1; onset in teens to mid-20s (rare after 40 y)	Progressive limitation of spinal motion, a.m. stiffness, buttock pain, "bamboo spine," ⊕ Schober test
Psoriatic arthritis (PsA)	♂ = ♀; peak incidence 45–54 y; seen in 20–30% of Pts w/ psoriasis	In ~15% arthritis precedes skin findings by yrs; does not correlate with psoriasis activity; a/w HIV
Reactive arthritis (ReA)	♂ >> ♀; 20–40 y; 10–30 d after **GI or GU infxn*** in genetically susceptible host	Arthritis, urethritis, and conjunctivitis. Most resolve w/in 12 mo.
IBD-associated arthritis	♂ = ♀; seen in 20% of IBD Pts; Crohn's > UC	Type I <5 joints: correlates w/ IBD activ. Type II >5 joints or axial disease: does not correlate w/ IBD activity

*GU: *Chlamydia*, *Ureaplasma urealyticum*; GI: *Shigella*, *Salmonella*, *Yersinia*, *Campylobacter*, *C. diff*.

Major clinical manifestations (*JAMA* 2025;333:408)

- **Inflammatory back pain:** SI joints (**sacroiliitis**), apophyseal joints of spine
  characterized by **IPAIN** (Insidious onset, Pain at night, Age of onset <40 y, Improves w/ exercise/hot water, No improvement w/ rest), a.m. stiffness, *responsive to NSAIDs*
- **Peripheral arthritis:** typically asymmetric, oligoarticular, large joints, lower > upper limbs; however, can be symmetric & polyarticular (thus, mimic RA), espec. psoriatic arthritis
- **Enthesitis:** inflammation at site of tendon/ligament insertion into bone, espec. Achilles, plantar fascia (calcaneal insertion), pre-patellar, elbow epicondyles
- **Rigidity of spine:** bamboo spine by X-ray, ankylosis due to progressive growth of bony spurs that bridge intervertebral disc
- **Dactylitis:** "sausage digit," inflammation of entire digit (joint + tenosynovial inflamm)
- **Uveitis:** anterior uveitis *most common extra-articular manifestation* in seronegative SpA; usually unilateral and p/w pain, red eye, blurry vision, photophobia

Distinguishing Features				
	Axial Predom	*Peripheral Predominant*		
Feature	**Ankylosing Spondylitis**	**Psoriatic**	**Reactive**	**IBD Assoc**
Axial involv.	100%	20–40%	40–60%	5–20%
Sacroiliitis	Symmetric	Asymm	Asymm	Symmetric
Periph involv.	Less common ~50%	Frequent	Frequent	Frequent
Peripheral distribution	Lower > upper	Upper > lower (vide infra)	Lower > upper	Lower > upper
HLA-B27	80–90%	20%	50–80%	5–30%
Enthesitis	Frequent	Frequent	Frequent	Rare
Dactylitis	Uncommon	Common	Common	Uncommon
Ocular	Uveitis in 25–40%	Conjunctivitis, uveitis, episcleritis	**Conjunctivitis** (noninfectious), uveitis, keratitis	Uveitis
Skin	None	**Psoriasis;** nail pitting and onycholysis	Circinate balanitis, keratoderma blennorrhagica	*E. nodosum*, pyoderma gangrenosum
Imaging	Bamboo spine (symm syndes.)	"Pencil-in-cup" DIP deformity	*Asymmetric* syndesmophytes	Periph dis. rarely erosive

Clinical assessment (*Nat Rev Rheumatol* 2021;17:109)

- **Seronegative:** rheumatoid factor and other autoantibodies usually ⊖; ± ↑ ESR/CRP
- **HLA-B27:** nonspecific, common in general population (6–8%); most useful when high clinical suspicion but nl imaging; ⊕ 90% of Pts w/ AS, but only 20–80% in other SpA
- **Axial disease physical exam**
  The following are not specific, but useful in monitoring disease during Rx:
  Lumbar flexion deformity assessed by **modified Schober's test** (⊕ if <5 cm ↑ in distance between a point 5 cm below the lumbosacral jxn and another point 10 cm above, when going from standing to maximum forward flexion)
  T-spine mobility (extension) and kyphosis severity measured by **occiput-to-wall distance** (although occiput-to-wall distance also increased in osteoporotic kyphosis)
- **Infectious evaluation for reactive arthritis** (⊖ studies do not r/o)
  GU: U/A, PCR of urine and/or genital swab for *Chlamydia;* urethritis usually due to *Chlamydia* infxn preceding arthritis, but can also see sterile urethritis post dysentery
  GI: stool Cx, *C. diff.* toxin
  Other: Consider HIV in w/u of reactive (or psoriatic) arthritis
- **Radiology**
  MRI preferred for *early* detection of inflammation (sacroiliitis)
  Plain films detect late structural changes (SI erosions/sclerosis) Calcific. of spinal ligaments w/ bridging symmetric syndesmophytes ("bamboo spine") Squaring and generalized demineralization of vertebral bodies ("shiny corners")

Descriptions of skin manifestations

- **Psoriasis**: erythematous plaques with sharply defined margins & thick silvery scale
- **Circinate balanitis:** shallow, painless ulcers of glans penis and urethral meatus

- **Keratoderma blennorrhagica:** hyperkeratosis of palms/soles, scrotum, trunk, scalp
- **Erythema nodosum:** red tender nodules in subcutan. fat (panniculitis), typically on shins Ddx includes idiopathic, infxn, sarcoid, drug rxn, vasculitis, IBD, lymphoma
- **Pyoderma gangrenosum:** neutrophilic dermatosis → painful ulcers w/ violaceous border Ddx: idiopathic, IBD, RA, malignancy, or heme disorder (MGUS, MDS, polycyth. vera)

Psoriatic arthritis subtypes (*Lancet* 2018;391:2273 & 2285; *Nat Rev Dis Primers* 2021;7:59)

- **Mono/oligoarticular** (large or DIP joint, dactylitic digit): most common initial manifestation
- **Polyarthritis** (small joints of the hands/feet, wrists, ankles, knees, elbows): indistinguishable from RA, but often asymmetric
- **Arthritis mutilans:** severe destructive arthritis with bone resorption, esp. hands
- **Axial disease:** often unilateral/asymmetric sacroiliitis
- **DIP-limited:** good correlation with nail pitting and onycholysis

Treatment approach (*Arthritis Care Res* 2019;71:2 & 1285; *NEJM* 2021;385:628)

- Untreated disease may lead to irreversible structural damage and associated ↓ function
- Early physiotherapy beneficial (*Br J Sports Med* 2020;54:292)
- Tight control of inflammation may improve outcomes (eg, in PsA; *Lancet* 2015;386:2489)
- **NSAIDs:** 1st line; rapidly ↓ stiffness/pain; may modify disease course but a/w GI and CV toxicity; may exacerbate IBD
- **Intra-articular corticosteroids** in mono- or oligoarthritis; limited role for systemic steroids, espec. for axial disease
- **Conventional DMARDs** (eg, MTX, SSZ, leflunomide): no efficacy for axial disease or enthesitis; may have role in peripheral arthritis, uveitis, and extra-articular manifestations
- **Anti-TNFs:** effective for both axial and peripheral SpA, improves function, and may slow progression of structural changes; adalimumab or infliximab preferred if eyes involved
- **Anti-IL-17A** (secukinumab, ixekizumab) and **anti-17A/17F** (bimekizumab) for AS and axial and peripheral PsA. Do not use if c/f IBD as may cause IBD exacerbation/onset (*Lancet* 2023;401:25 & 38; *Ann Rheum Dis* 2023;82:515 & 1404).
- **Anti-IL-12/23** (p40) (ustekinumab) and **anti-IL-23** (p19) (guselkumab, risankizumab) for axial & peripheral PsA (*Ann Rheum Dis* 2022;81:225 & 351) but not axial SpA
- **Abatacept** (CTLA4-Ig) for PsA. Less effective for psoriasis (*Ann Rheum Dis* 2017;76:1550).
- **PDE-4 inhibitor** (apremilast): effective in PsA refractory to conventional DMARD or as first-line (*Rheumatology* 2018;7:1253); a/w GI side effects, wt loss, depression
- **JAK inhibitor:** for conventional DMARD- or anti-TNF-resistant peripheral and/or axial SpA (*NEJM* 2017;377:1525 & 1537; 2021;384:1227)
- **Other:**
  - Abx for ReA if active GU infxn, but not typically for uncomplic. enteric infx. Prolonged abx for refractory *Chlamydia* ReA controversial.
  - Involve ophtho if suspect eyes affected (may need steroid drops or intravitreal injection)
  - Treat underlying IBD when appropriate

CONNECTIVE TISSUE DISEASES

Approx Prev of Autoantibodies in Rheumatic Diseases											
Disease	**ANA**	**dsDNA**	**Sm**	**Ro/La**	**Scl-70**	**RNA PIII**	**Centr**	**Jo-1**	**U1-RNP**	**RF**	**CCP**
SLE	≥95	75	20	25	⊖	⊖	⊖	⊖	45	35	15
Sjögren's	≥95	rare	⊖	45	⊖	⊖	⊖	⊖	rare	>75	10
dcSSc	>90	⊖	⊖	rare	40	20	rare	⊖	rare	30	10
lcSSc	>90	⊖	⊖	rare	10	rare	60	⊖	rare	30	15
IM	75–95	⊖	⊖	⊖	rare	⊖	⊖	25	⊖	15	15
MCTD	≥95	⊖	⊖	rare	⊖	⊖	⊖	⊖	100	50	10
RA	40	⊖	⊖	⊖	⊖	⊖	⊖	⊖	⊖	70	70

Centr, centromere; dcSSc, diffuse cutaneous systemic sclerosis; lcSSc, limited cSSc; IM, inflammatory myopathies; RF, rheumatoid factor; Sm, Smith (*Primer on the Rheumatic Diseases*, 12th ed, 2001; *Lancet* 2013;382:797; *J Rheumatol* 2015;42:558)

- Only order auto-Ab testing if clinical suspicion for CTD. The presence of auto-Ab without characteristic clinical findings ≠ diagnosis; auto-Ab alone do not define a particular CTD.
- Overlap syndromes may be reflected by multiple autoantibodies

see "Systemic Lupus Erythematosus" and "Rheumatoid Arthritis" for those diseases

Systemic Sclerosis and Scleroderma Disorders

Definition & epidemiology (*Lancet* 2023;401:304)

- **Scleroderma** refers to the presence of tight, thickened skin
- **Localized scleroderma:** *morphea* (plaques of fibrotic skin), *linear* (fibrotic bands), "*en coup de sabre*" (linear scleroderma on one side of scalp and forehead ≈ saber scar)
- **Systemic sclerosis (SSc)** = scleroderma + internal organ involvement. High mortality.
  SSc *w/ limited cutaneous disease (lcSSc):* formerly CREST syndrome (vide infra)
  SSc *w/ diffuse cutaneous disease (dcSSc):* often rapidly progressive skin thickening
  SSc *sine scleroderma* (visceral disease without skin involvement, rare)
- Overlap: systemic sclerosis + SLE, RA, idiopathic inflammatory myositis or Sjögren's
- Peak onset **age 30–50;** ♀ > ♂ (4:1). Often earlier/more severe in African Americans.
- <6/100,000 annual SSc incidence worldwide; lcSSc incidence ~2× that of dcSSc
- Pathogenesis: endothelial injury (vasculopathy), autoimmunity, fibroblast dysfunction, fibrosis. Pathogenicity of autoAb (eg, anti-Scl-70) remains uncertain.

ACR/EULAR SSc classification criteria (*Ann Rheum Dis* 2013;72:1747)

- Sufficient for dx: skin thickening of fingers of both hands extending proximal to MCPs
- Other criteria: Raynaud's, SSc auto-Ab, pulm hypertension (PHT) or ILD, abnormal nailfold capillaries, telangiectasia, fingertip lesions (ulcers/scars), skin thickening distal to MCPs
- **Rule out other etiologies** for thick skin (± bx): diabetes (scleredema), GVHD, amyloid, scleromyxedema, hypothyroid, nephrogenic systemic fibrosis, eosinophilic fasciitis

Clinical Manifestations of Systemic Sclerosis	
Skin	"Puffy" hands; tightening and thickening of extremities, face, trunk; sclerodactyly. Immobile, pinched, "mouse-like" facies; "purse-string" mouth. Calcinosis cutis (subcutaneous calcification); nailfold capillary dilatation & dropout; telangiectasias. Carpal tunnel syndrome.
Arteries	**Raynaud's phenomenon** (80%); digital or visceral ischemia

Renal	**Scleroderma renal crisis (SRC)** = abrupt onset severe HTN (*relative to baseline*), MAHA (↓ plt, acute renal failure, relatively bland UA). Renal bx not required, but would show "onion-skin" hypertrophy of arteries & arterioles. ACEI effective but 40% still progress to ESRD and 5-y mortality is 40% (*QJM* 2007;100:485). Risks: dcSSc, early disease (2/3 of cases in 1st yr), >15 mg/d prednisone, RNA Pol III Ab, tendon friction rubs.
GI (>80% of Pts)	GERD/erosive esophagitis, esophageal dysmotility (dysphagia, aspiration), gastric antral vascular ectasia (GAVE), gastric dysmotility, small intestinal dysmotility (malabsorption, bacterial overgrowth, bloating)
MSK	Arthralgias/arthritis; myositis; joint contractures; tendon friction rubs
Cardiac	Myocardial fibrosis; pericardial effusion; conduction abnormalities; CAD
Pulm	**Majority have pulmonary involvement**; leading cause of hosp. & mortality **ILD:** typically NSIP and develops w/in 4 y. ↑ risk w/: anti-Scl-70, nucleolar ANA, dcSSc, African Amer., ♂, first 5–7 y of dx, ↑ CRP. **Pulm. arterial hypertension (PAH)**: typically after many yrs
Endo	Amenorrhea and infertility common; thyroid fibrosis ± hypothyroidism

SSc Subgroup Comparison		
	Limited (lcSSc)	**Diffuse (dcSSc)**
General		Fatigue, weight loss
Skin	Thickening on extremities *distal to* elbows/knees and *face* only	Thickening of distal *and proximal* ext, face *and trunk*
Pulmonary	PAH (rapidly progressive) > fibrosis	Fibrosis > PAH
GI	Primary biliary cirrhosis	
Renal	SRC later in disease course	SRC earlier & more common
Cardiac		Restrictive cardiomyopathy
Other	**CREST syndrome** = **C**alcinosis, **R**aynaud's, **E**sophageal dysmotility, **S**clerodactyly, **T**elangiectasias	Raynaud's
Antibodies	Centromere (10–40%)	Scl-70, RNA Pol III (40%)
Prognosis	Survival >70% at 10 y	Survival 40–60% at 10 y

Diagnostic studies & monitoring (*Arthritis Rheumatol* 2024;76:1201)

- **Autoantibodies:** >95% Pts w/ auto-Ab; generally mutually exclusive
  - ⊕ **anti-Scl-70** (anti-topoisomerase I): diffuse SSc; ↑ risk pulm fibrosis
  - ⊕ **anti-centromere:** limited SSc; ↑ risk of severe digit ischemia and PHT
  - ⊕ **anti-RNA Pol III:** diffuse SSc; ↑ risk renal crisis; a/w cancer
  - ⊕ ANA (>90%), ⊕ RF (30%), ⊕ anti-U1-RNP a/w overlap syndrome

  Other: anti-Th/To (limited SSc), U3-RNP (PAH, myositis), PmScl (myositis–SSc overlap)
- At baseline: ✓ BUN/Cr & UA for proteinuria, PFTs (spirometry, lung volumes, D_LCO), high- res chest CT (if diffuse disease), TTE (RVSP for PHT), RHC if ↑ RVSP or suspect PHT
- Monitoring: modified Rodnan Skin Score, PFTs q3–6m for 1st y then space out if stable; ambulatory S_pO_2 q3–12mo; HRCT; NTproBNP
- Close monitoring of blood pressure as HTN could indicate scleroderma renal crisis

Treatment (*Ann Rheum Dis* 2017;76:1327; *Nat Rev Rheumatol* 2023;19:212)

- *Minimize steroid exposure to reduce risk of renal crisis*
- ILD: MMF (↓ toxicity vs. CYC), tocilizumab (early), or RTX. Refractory ILD: nintedanib (anti-fibrotic), CYC (*NEJM* 2019;380:2518; *Lancet Respir Med* 2016;4:708 & 2020;8:963; *Arthritis Rheumatol* 2024;76:1182).
- PAH: pulmonary vasodilators (see "Pulm Hypertension"); early Rx a/w better outcomes
- Renal crisis: **ACEI** (not ARB) for Rx, not prophylaxis (*Semin Arthritis Rheum* 2015;44:687)
- GI: PPI/H2-blockers for GERD; promotility agents & antibx for bacterial overgrowth
- Cardiac: NSAIDs ± colchicine superior to steroids for pericarditis
- Arthritis: acetaminophen, NSAIDs, HCQ, MTX
- Myositis: MTX, cautious low-dose steroids
- Skin. Localized (morphea): if sx/fxnal impairment → Rx w/ topical/intralesional steroids, tacrolimus, phototherapy. Systemic: MMF, MTX. If refractory: RTX, IVIG. CYC if severe (*NEJM* 2006;354:2655; *Lancet Respir Med* 2016;4:708). Raynaud's: vide infra.
- Auto-HSCT has shown promise in severe disease (*NEJM* 2018;378:35). Possibility of treatment-free durable remission with CAR-T cell Rx under study (*NEJM* 2024;390:687).

Raynaud's Phenomenon

Clinical manifestations & diagnosis (*Nat Rev Rheumatol* 2023;19:212)

- Episodic, reversible digital ischemia due to cold-induced vasospasm. Classically: **blanching** (white, ischemia) → **cyanosis** (blue, hypoxia) → **rubor** (red, reperfusion); color Δ usually well demarcated; affects fingers/toes, rarely ears or nose.
- Ddx: **arterial disease** (athero, Buerger's, thrombosis/APS), trauma, pernio/chilblains, erythromelalgia, **cryoprecipitant/agglutination** (cryo, Waldenström's, cold agglutination), drugs (ergopeptides, cocaine, estrogen, other vasoconstrictors)

Primary vs. Secondary Raynaud's Phenomenon

	Primary (80–90%)	**Secondary (10–20%)**
Vessel wall	*Functionally* abnl	*Structurally* abnl
Etiologies	Idiopathic	SSc, SLE, PM–DM, MCTD, Sjögren's, RA
Epidemiol.	15–40 y; ♀ > ♂ (5:1)	>40 y
Clinical	Mild symptoms. *No tissue injury; spares thumb.*	More severe symptoms; **tissue ischemia & injury** (eg, digital ulcers); can be assoc w/ systemic sx; may affect thumb or prox limbs
Auto-Ab	⊖ CTD antibodies	Depends on etiology, CTD Ab often ⊕
Nailfold	Normal capillaroscopy	**Dropout and enlarged or distorted loops**

Treatment (*Lancet* 2023;401:304)

- All: **avoid cold**, maintain warmth of digits & core; avoid cigarettes, sympathomimetics, extremity trauma; abx for infected ulceration
- **Mild–mod: long-acting CCB**, topical nitrates, SSRI, ± ASA
- Severe: inhibitors of PDE-5 or endothelin receptor, digital sympathectomy, IV prostaglandin

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Idiopathic Inflammatory Myopathies (Myositis)

Subclassification & epidemiology (*Nat Rev Rheumatol* 2023;19:695)

- Typically feature skeletal muscle inflammation & weakness w/ variable extramuscular involvement, but amyopathic presentations and syndromes (eg, MDA5) recognized
- **Dermatomyositis** (DM): classic skin rashes, a/w **malignancy** (24%); incidence 15/mill/y
- **Polymyositis** (PM): similar to DM w/o rash; incidence <1/mill/y; peak onset 40s–50s; ♀ >♂
- **Immune-mediated necrotizing myositis** (IMNM): risk factors: statin exposure (⊕ anti-HMGCR), CTD, possibly cancer, rarely viral infection; incidence unclear
- **Anti-synthetase syndrome:** characteristic clinical syndrome (vide infra), aminoacyl-tRNA synthetase autoAbs. Some classify as a DM/PM subgroup; others consider it distinct.
- **Inclusion body myositis** (IBM): age >50; ♂ > ♀; incidence ~8/million/y; often *misdx as PM*
- Ddx: drug-induced toxic myopathy (statins, cocaine, steroids, colchicine); infxn (HIV, EBV, CMV); metabolic (hypothyroid, hypo-K, hypo-Ca); neuromuscular dis. (eg, myasthenia gravis); glycogen storage disease; mitochondrial cytopathy; muscular dystrophy

Clinical manifestations

- **Muscle weakness:** typically gradual onset (wks to mos) but often accelerated in IMNM (days to wks) and more insidious (yrs) in IBM; progressive and painless
  - DM/PM/IMNM: **proximal and symmetric**; difficulty climbing stairs, arising from chairs, brushing hair; fine motor skills (eg, buttoning) lost late
  - IBM: weakness may be asymmetric, distal and proximal, and involve facial muscles
- **DM skin findings:** may precede myositis; bx indistinguishable from lupus rash
  - *Gottron's papules*: seen in >80% of Pts & pathognomonic; violaceous, often scaly, areas symmetrically over dorsum of PIP and MCP joints, elbows, patellae, medial malleoli
  - *Heliotrope rash*: purplish discoloration over upper eyelids ± periorbital edema
  - *Poikiloderma*: red or purple rash w/ areas of hyper and hypopigmentation mostly on sun-exposed areas; upper back (shawl sign), neck & chest (V sign), and hips (Holster sign)
  - *Mechanic's hands:* cracking, fissuring radial side of digits and can include pigmentation along palmar crease; a/w antisynthetase syndrome; also seen in PM
- **Pulmonary:** acute alveolitis, **ILD**; rarely resp muscle weakness; aspiration
  - *Antisynthetase syndrome*: rapidly progressive ILD, fever, weight loss, Raynaud's, mechanic's hands, arthritis, myositis
  - *MDA5-assoc. DM:* amyopathic, rapidly progressive ILD, painful palmar papules, ulcerated Gottron's papules/sign. ~50% mortality if RP-ILD.
- **Cardiac:** (33%): often asx; conduction abnl; myo/pericarditis; HF uncommon; ↑ CK-MB/Tn
- **GI:** dysphagia, aspiration
- **Polyarthralgias or polyarthritis:** nonerosive, small > large
- **Raynaud's:** DM, antisynthetase or overlap syndromes. A/w abnormal nailfold capillaries.

Diagnostic studies (*Arthritis Rheumatol* 2024;76:1201; *Nat Rev Rheumatol* 2025;21:46)

- ↑ **CK** (rarely >100,000 U/L, can be ↑↑↑ in NM), aldolase, SGOT, LDH; ± ↑ ESR & CRP
- **AutoAbs**: often order as panel. ⊕ ANA in many but not all (some Ag cytoplasmic).
  - *DM:* anti-TIF1 γ or anti-NXP2, anti-Mi-2, anti-SAE, anti-MDA5, others
  - *IMNM:* anti-HMGCR (a/w statin use), anti-SRP (a/w severe disease, cardiac involvement)
  - *Antisynthetase syndrome:* auto-Ab to Jo-1 (20% of all IIM), PL-12, PL-7, OJ, EJ, others
  - *IBM:* anti-cN1A in ~50% (but not specific; seen in other rheumatic diseases)
- **MRI** of proximal muscles (edema/inflammation, atrophy), **EMG**; may guide biopsy site
- **Muscle biopsy:** mononuclear infiltrate; fiber necrosis, degeneration/regeneration
  - *DM: immune complex deposition in vessels* with complement activation; inflammation (CD4 and B cells) surrounding fascicles and blood vessels w *perifascicular atrophy*
  - *PM:* CD8 *T-cell inflammation invading muscle fascicles* (endomysial)
  - *IMNM:* necrotic fibers w/ macrophages; relative paucity of inflammatory infiltrate
  - *IBM:* prominent inflammatory infiltrate, *rimmed vacuoles* and eosinophilic inclusions
- **High-res CT chest, PFTs** if ↑ ILD risk (anti-synth., anti-MDA5, anti-Ro52, dyspnea, etc.)

Treatment (*NEJM* 2022;387:1264; *Lancet Rheumatol* 2024;6:e115; *Arthritis Rheumatol* 2024;76:1182)

- Immunosuppression not effective for IBM. For all others:
- **Steroids** (prednisone 1 mg/kg); MTX, AZA, or MMF as steroid-sparing; physical therapy
- For resistant (30–40%) or severe disease: IVIG, rituximab, combination DMARD, CYC
- IVIG w/ pulse steroids acutely for life-threatening esophageal or resp muscle involvement
- ILD: MMF, AZA, RTX, or CNI ± steroids. Refractory: JAKi, CYC, nintedanib, IVIG.
- Rapidly prog. ILD (eg, MDA5): IV steroids & 1 or 2 of: RTX, CYC, IVIG, MMF, CNI, JAKi.
- ✓ **for occult malignancy** (esp. DM); monitor respiratory muscle strength (spirometry)
- IMNM: stop statin; steroids + MTX, RTX, or IVIG
- Photoprotection (DM)
- Treatment-free remissions seen in early autologous CAR-T cell studies (*NEJM* 2024;390:687)

Myositides, Myopathies, and Myalgias

Disease	Weakness	Pain	↑ CK	↑ ESR	Biopsy
DM/PM/IMNM	⊕	⊖	⊕	±	as above
IBM	⊕	⊖	⊕	⊖	as above
Hypothyroidism	⊕	±	⊕	⊖	mild necrosis inflam, atrophy
Steroid-induced	⊕	⊖	⊖	⊖	atrophy
PMR	⊖	⊕	⊖	⊕	normal
Fibromyalgia	⊖	⊕	⊖	⊖	normal

Sjögren's Syndrome

Definition & epidemiology (*Nat Rev Rheumatol* 2024;20:158)

- Chronic dysfxn of **exocrine glands** (eg, salivary/lacrimal) due to lymphoplasmacytic infiltration; extraglandular manifestations common in primary form
- Can be primary or secondary (a/w RA, scleroderma, SLE, PM, hypothyroidism, HIV)
- >1/10,000 prevalence with 9:1 ♀:♂ ratio; typically presents between age 40 & 60

Clinical manifestations

- **Dry eyes** (keratoconjunctivitis sicca): ↓ tear production; burning, scratchy sensation
- **Dry mouth** (xerostomia): difficulty swallowing, dental caries, xerotrachea, thrush
- **Parotid gland enlargement:** intermittent, painless, typically bilateral
- **Vaginal dryness** and **dyspareunia**
- **Recurrent nonallergic rhinitis/sinusitis** due to upper-airway gland involvement
- **Extraglandular:** arthritis, interstitial nephritis, type I RTA, cutaneous vasculitis, PNS > CNS neurologic disease (20%), ILD (lymphocytic interstitial PNA), PBC
- Lymphoproliferative: ↑ risk of NHL in 1° Sjögren's (MALT lymphoma most commonly)
- Neonatal lupus: fetal skin rash or heart block (maternal anti-Ro > La)

Diagnostic studies

- Autoantibodies: ⊕ ANA (50–80%), ⊕ RF (60–80%)
  Primary Sjögren's: ⊕ **anti-Ro** (anti-SSA, ~50%) ± **anti-La** (anti-SSB, ~30%)
  ✓ anti-Ro/La even if ANA negative as Ro is a cytoplasmic antigen
- **Schirmer test:** filter paper in palpebral fissures to assess tear production
- **Corneal staining**: assess for devitalized epithelium of cornea/conjunctiva

- **Biopsy** of minor salivary (typically), labial, lacrimal, or parotid gland: lymphocytic infiltration

Classification criteria (≥4 points 96% Se & 95% Sp; *Arthritis Rheumatol* 2017;69:35)

- 3 points: ⊕ anti-Ro; labial saliv. gland bx w/ lymphocytic sialadenitis & score ≥1 foci/4 mm^2
- 1 point: abnormal ocular staining score ≥5; Schirmer's test ≤5 mm/5 min; unstimulated salivary flow rate of ≤0.1 mL/min

Management (*Arthritis & Rheumatol* 2020;72:529; *Nat Rev Rheumatol* 2024;20:473)

- Ocular: artificial tears, cyclosporine eyedrops, autologous tears
- Oral: sugar-free gum, lemon drops, saliva substitute, hydration, pilocarpine, cevimeline
- Systemic: depends on extraglandular manifest.; NSAIDs, steroids, DMARDs, rituximab
- HCQ & fetal cardiac monitoring during pregnancy if ⊕ anti-Ro or La

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Mixed Connective Tissue Disease (MCTD)

Definition

- High-titer anti-U1-RNP with features of **SLE**, **systemic sclerosis**, inflammatory **arthritis**, and/or **inflammatory myopathy.** Often evolve to a dominant phenotype of SLE or SSc.
- Different from undifferentiated CTD (UCTD): nonspecific symptoms that fail to meet criteria for any CTD; 30% of UCTD develop CTD over 3–5 y (usually SLE)

Clinical & laboratory manifestations (*Rheumatology* 2018;57:255)

- **Raynaud's phenomenon**, hand edema ("puffy hands"), sclerodactyly, RA-like **arthritis** w/o erosions, **pulmonary hypertension**, ILD, pericarditis
- Lower risk for SSc-like renal crisis or severe GN
- ⊕ ANA (>95%); ⊕ RF (50%); requires ⊕ **anti-U1-RNP** but *not* specific (seen in ~50% SLE)

Management (*Arthritis Rheumatol* 2024;76:1182 & 1201)

- as per manifestations of specific rheumatic diseases detailed above
- Raynaud's, dysphagia, or other SSc feature: consider PFTs & HRCT to assess for ILD

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Definition and epidemiology (*Nat Rev Rheumatol* 2021;17:515; *JAMA* 2024;331:1480)

- Multisystem autoimmune disease with a broad spectrum of clinical manifestations associated with antinuclear antibody (ANA) production and immune complex deposition
- Prevalence 5–35/10,000 in U.S.; predominantly affects women in 2nd to 4th decade
- ♀:♂ ratio = 8:1; African Americans affected 2–4× as often as Caucasians
- Complex genetics; some HLA association; rarely C1q & C2 deficiency

Classification Criteria (Adapted with permission from *Ann Rheum Dis.* 2019;78(9):1151–1159.) for ***research/classification*** not dx		
Required criteria: **ANA titer ≥1:80** AND ≥**10** points (at least one clinical):		
Clinical Domains* (points**)		

Renal	**Hematologic**	**Neuropsychiatric**
• proteinuria >0.5 g/d (4) • class II or V nephritis (8) • class III or IV nephritis (10)	• leukopenia (3) • thrombocytopenia (4) • autoimm. hemolytic anemia (4)	• delirium (2) • psychosis (3) • seizure (5)
Mucocutaneous	**Serosal**	**Musculoskeletal**
• non-scarring alopecia (2) • oral ulcers (2) • discoid lupus (4); subacute (4) or acute (6) cutaneous lupus	• pleural/pericardial effusion (5) • acute pericarditis (6)	• joint involvement (6)
		Constitutional • fever (2)
Immunology Domains (points*)		
Antiphospholipid antibodies	**Complement proteins**	**SLE-specific Abs**
• anti-CL, anti-B2GP1, or a lupus anticoagulant (2)	• low C3 or C4 (3) • low C3 and C4 (4)	• anti-dsDNA or anti- Smith (6)

*Other notable SLE sx: fatigue, photosensitivity. **Within a domain, only score the highest weighted criterion.

Autoantibodies in SLE (*Nat Rev Rheumatol* 2020;16:565)

Auto-Ab	Frequency (approx)	Clinical Associations	Timeline
ANA	95–99% if active disease Homogeneous or speckled	Any or all of broad spectrum of clinical manifestations Sensitive but not specific	May appear yrs before overt disease
Ro **La**	15–35% ⊕ anti-Ro may be seen w/ ⊖ or low titer ANA	Sjögren's/SLE overlap Neonatal lupus; photosens.; subacute cutaneous lupus	
dsDNA	70%; ~95% Sp	Titers often parallel disease activity; nephritis	Appears mos before or at dx, but may become ⊕ after dx
Sm	30%; very specific for SLE	Nephritis	
U1-RNP	40%	MCTD; Raynaud's; Tend *not* to have nephritis	
Histone	90% in DLE; 60–80% in SLE	Mild arthritis and serositis	At diagnosis

Workup

- Autoantibodies: ANA, if ⊕ → ✓ anti-dsDNA, anti-Sm, anti-Ro, anti-La, anti-U1-RNP
- CBC, APLA (20–40% ⊕; ACL, B2GP1, lupus anticoagulant), C3 & C4 (↓ with SLE activity)

- BUN, Cr, UA, urine sed, spot microalb:Cr ratio or 24-h urine for CrCl and protein
- In follow-up: ✓ for proteinuria q6–12m (q3–6m if nephritis hx), activity (C3, C4, dsDNA)
- If ↓ GFR, active sediment, hematuria, or proteinuria (>0.5 g/dL) → renal bx to guide Rx

Treatment (*Ann Rheum Dis* 2024;83:15; *Lancet* 2024;403:2326; *Arthritis Rheumatol* 2025;doi:10.1002/art.43212)		
Agent	**Indication**	**Adverse Effects**
Hydroxychloroquine (HCQ)	**All SLE. ↓ flares & mortality**. Potential monoRx of arthritis, serositis, skin disease.	Retinal tox (<1%), Stevens–Johnson, myopathy. *Not immunosuppressive*.
NSAIDs	Arthritis, myalgias, serositis	Gastritis, UGIB, renal/CV tox
Corticosteroids	Low dose for arthritis, serositis; high (0.5–1 mg/kg/d) ± pulse (1 g/d × 3 d) for major dis. (renal, CNS, heme). Minimize as able.	Adrenal suppression, diabetes, cataracts, osteopenia, avascular necrosis of bone, myopathy
Mycophenolate (MMF)	**Nephritis**; nonrenal disease refractory to HCQ	Cytopenias, ↑ LFTs, diarrhea, teratogen
Cyclophosphamide (CYC)	**Severe organ-threatening nephritis or CNS disease** (induction, minimize exposure)	Cytopenias, infertility/teratogen, myeloprolif. dis., hemorrhagic cystitis, bladder cancer, infxn
Azathioprine (AZA)	Nephritis, non-renal dis. refractory to HCQ	Myelosuppr. (✓TPMT), ↑ LFTs, lymphoprolif. dis.
Methotrexate (MTX)	Arthritis (preferred over MMF/AZA), rash, serositis	Myelosuppression, alopecia, hepatotoxicity, stomatitis, pneumonitis, teratogen
Cyclosporine (CsA) or **tacrolimus** (calcineurin inhib, CNI)	Nephritis	Gingival hyperplasia (CsA), HTN, hirsutism, CKD, anemia, neurotoxicity
Voclosporin (CNI, *Lancet* 2021;397:2070)	Nephritis. Add to MMF/steroids; ↑ renal response, ↓ steroid.	HTN, ↓ GFR, diarrhea. Stable PK, ∴ no need to ✓ levels.
Belimumab (*NEJM* 2013;368:1528 & 2020;383:1117)	Arthritis, serositis, skin disease (esp. if ⊕ dsDNA or ↓ C3/C4). Nephritis (↑ renal response).	B-cell depletion but ↓ immuno-suppression vs. RTX. Mood Δs.
Rituximab (RTX), obinutuzumab (obi) (anti-CD20)	RTX: ITP, AIHA, refractory SLE (including nephritis) Obi: nephritis (*NEJM* 2025;392:1471)	Infusion reaction, serum sickness, PML, infection
Anifrolumab (anti-type 1 IFN receptor, *NEJM* 2020;382:211)	Mod–severe dis.; particularly effective for skin > MSK/mucocut. (*Lancet Rheumatol* 2023;4e:282)	Infection (PNA, zoster), hypersensitivity reaction

- Reduce risk factors for flares/activity: sun exposure (UV-mediated DNA damage), smoking
- Possible treatment-free remissions with CAR-T cell therapy under study (*NEJM* 2024;390:687)

Lupus Nephritis—40% affected (*Kidney Int* 2024;105:S1; *Arthritis Rheumatol* 2025;doi:10.1002/art.43212)		
Class	**Presentation**	**Treatment (all benefit from HCQ)**
I: Min. mesangial	Normal U/A & eGFR	No specific treatment
II: Mesangial prolif	Micro	No specific treatment ± ACEI

	hematuria/proteinuria	
III: Focal proliferative	Hematuria/proteinuria, ± HTN, ↓ GFR, ± nephrotic	**Triple Rx**: **[MMF** + **belimumab]** *or* **[MMF** + **CNI** (>3 g proteinuria/d)**]** *or* [low-dose CYC & belimumab] above + **steroid** pulse/taper
IV: Diffuse proliferative	Hematuria/proteinuria and HTN, ↓ GFR, ± nephrotic	
V: Membranous (can coexist with class III or IV)	Proteinuria, nephrotic	ACEI. If >1 g/d proteinuria, **triple Rx**: MMF + CNI + steroids. If <1 g/d, steroids + MMF, AZA, or CNI.
VI: Adv. Sclerotic	ESRD	Transplant, dialysis

- Goal to taper steroids from initial 0.5 mg/kg/d to <5 mg/d prednisone equivalents by 6 m
- Continue nephritis Rx 3–5 y after complete renal response (proteinuria <0.5 g/g, stable GFR)
- Attention to mgmt of associated ⊕ APLA or APLS, particularly during pregnancy (see Hematology Ch; *Arthritis & Rheumatol* 2023;75:1687; 2020;72:529)

Prognosis (*JAMA* 2024;331:1480)

- Overall mortality 3× higher than general population, higher in Blacks
- Leading causes of morbidity/mortality: **infection**, CV events, **renal failure** (nephritis remission achieved in <50%; >10% end up w/ ESRD), neurologic events, thrombosis

Drug-induced lupus (DLE) (*Drug Saf* 2017;16:1255; *Autoimmun Rev* 2018;17:912)

- Many drugs: **procainamide**, **hydralazine**, penicillamine, minocycline, INH, methyldopa, quinidine, chlorpromazine, diltiazem, **anti-TNF** (esp. infliximab), interferons
- Abrupt onset; generally mild sx (arthritis, serositis, rash); nephritis, discoid rash rare; prevalence ♀:♂ = 1:1
- ⊕ Anti-histone (95%) (may be ⊖ in anti-TNF); ⊖ anti-dsDNA (often ⊕ in anti-TNF cases, even w/o manifestations of DLE) & ⊖ anti-Sm; normal complement levels
- Usually reversible w/in 4–6 wk after stopping medication

IGG4-RELATED DISEASE

Definition & etiology (*NEJM* 2012;366:539; *Nat Rev Rheumatol* 2020;16:702)

- Characterized by tumor-like inflammatory lesions that can affect nearly any organ
- ♂ > ♀, mean age ~ 60. Incidence ~1/100,000 per y.

Clinical manifestations (*Arthritis Rheumatol* 2020;72:7; *Lancet Rheumatol* 2024;6:e469 & 481)

- Commonly pancreatitis, aortitis, cholangitis, sialadenitis, thyroiditis, dacryoadenitis, orbital myositis ± pseudotumor, retroperitoneal fibrosis, renal and lung involvement
- Insidious progression; multiple lesions may be present synchronously or metachronously

Diagnosis and management (*Lancet Rheumatol* 2019;1:e55; *NEJM* 2024;392:1168)

- **Biopsy:** lymphoplasmacytic infiltrate, ↑ IgG4+ cells, storiform fibrosis, obliterative phlebitis
- ↑ serum IgG4 (Se 90%, Sp 60%); may have low C3 and/or C4, elevated IgE
- Highly responsive to steroids but relapses. B-cell-depleting Rx effective (*NEJM* 2025;392:1168).

VASCULITIS

Overview

- Inflammation w/in blood vessel walls causing end-organ damage often a/w systemic sx; may be primary or secondary (eg, infection, malignancy) in etiology
- Classified by size of *predominant* vessel affected (*Arthritis Rheum* 2013;65:1); distribution in vessel size affected not uncommon
- Clinical manifestations relate to size of vessels involved; constitutional sx (low-grade fever, fatigue, weight loss, myalgias, anorexia) common to all

Distinguishing Characteristics of Vasculitis Subtypes

	Large Vessel		*Medium Vessel*	*Small Vessel*	
	TAK	**GCA**	**PAN**	**ANCA-Assoc.**	**IC**
Epi	Young, ♀ > ♂	Elderly, ♀ > ♂	Middle-aged to older	Variable	Variable
Renal	RAS/ HTN	None	Microaneurysms, RAS/HTN	GN	GN
Pulm	Rare	None	Rare	Nodules, DAH > ILD	DAH (cryo > IgA)
Periph Neurop	No	No	Yes	Yes	Yes
GI	Rare	Rare	Yes	No	IgA > Cryo
Skin	Rare	None	Ulcers/nodules	Palp. purpura	Palp. purpura
Granul	Yes	Yes	No	Yes, except MPA	No
Other		A/w PMR	Mesenteric aneurysms, testicular involv.	GPA: upper-airway EGPA: asthma	Cryo a/w HCV

TAK, Takayasu's; GCA, giant cell arteritis; PAN, polyarteritis nodosa; ANCA-assoc.: GPA, EGPA, MPA; IC, immune complex (eg, IgA, cryo); RAS, renal artery stenosis (→ ischemia/HTN); GN, glomerulonephritis

Large-Vessel Vasculitis

Takayasu's arteritis ("pulseless disease") (*Arthritis Rheumatol* 2021;73:1349)

- **Arteritis of aorta and its branches → stenosis/aneurysm** → claudication. Most often **subclavian** & **innominate arteries** (>90%); carotid, coronary, renal, or pulm a. (~50%).
- Epidemiology: most common in **Asia;** ♀:♂ ~9:1 in Japan but lower elsewhere; **age ≤40 y**. Prev 8/million in U.S. w/ ~4:1 ♀:♂ (*J Rheumatol* 2021;48:952; *Nat Reviews Rheum* 2022;18:22).
- Clinical: systemic inflammation w/ **fever**, arthralgias, wt loss. Vessel inflammation → pain/tenderness (**carotidynia** in >10%), **unequal BP/weak pulses in limbs**, **bruits**, limb claudication, renovascular HTN (>50%), Ao aneurysm ± AI, angina, syncope.
- Dx studies: ↑ ESR (75%), CRP; **arteriography** (MRA, CTA) → occlusion, stenosis, wall thickening, aneurysms; carotid U/S Doppler studies; PET-CT; **pathology** → focal panarteritis, cellular infiltrate with *granulomas* and giant cells (bx not required for dx)
- Rx: **steroids** + **DMARD** (eg, MTX or AZA) and/or **anti-TNF**; CYC (severe). ASA if critical cerebral stenosis. If surgical/endovascular revasc, preferably done in remission.
- Monitoring: MRA, CTA, or PET-CT; ESR/CRP

Giant cell arteritis (GCA) (*Arthritis Rheumatol* 2021;73:1349; *Ann Rheum Dis* 2022;81:1647)

- **Granulomatous arteritis** involving **aorta/branches**; predilection for **extracranial branches of carotids**, particularly temporal (thus also called **temporal arteritis**)
- Epidemiology: 90% >60 y, peak incidence at 70–80 y, extremely rare <50 y; ♀:♂ = 3:1. Incidence 1/10,000 of those age ≥50 (*Nat Reviews Rheum* 2022;18:22).
- Clinical: const. sx: **fevers**, fatigue, wt loss. **Temporal artery (TA)** → temporal **HA**; pulseless, thickened, or **tender TA;** tender scalp. Ophthalmic artery (20%) → **amaurosis fugax**, diplopia, **blindness** (ant. ischemic optic neuropathy). Facial artery → **jaw claudication**. Lg vessel → limb claudication, thoracic aorta aneurysm. Posterior CNS arteries → stroke.
- **Strong association w/ PMR**; ~50% of Pts w/ GCA ultimately received PMR diagnosis
- Dx: ↑ **ESR**, CRP (Se ~90%). **Doppler U/S** (halo sign), **temporal artery bx** (vasculitis, granulomas; Se ≤85%; consider bilat to ↑ yield [~5% discordant]). If negative bx or U/S but high suspicion, image aorta/large arteries (CTA, MRA, or PET).
- Rx: high-dose **steroids**. Start promptly if clinical suspicion, *do not await bx/path!* Have >2 wks to bx w/o Δ. Pred 40–60 mg/d w/ slow taper; IV pulse if vision threatened. ASA if critical carotid/vertebral stenosis. **Tocilizumab** (anti-IL-6R) or upadacitinib (JAKi) ↑ sustained remission, ↓ steroids (*NEJM* 2017;377:317; 2025;392:2013).
- **Polymyalgia rheumatica** (*NEJM* 2023;389:1263; *Lancet* 2023;402:1459)
  Prev 7/1000 of age ≥50. In 50% of GCA Pts; 15% of PMR Pts develop GCA. ♀:♂ ≈ 2.
  ↑ ESR, CRP; ***bilateral pain & morning stiffness*** (>30 m) of shoulders and/or hips; nl CK
  Rx: pred 12.5–25 mg/d; typically tapered over 1 y. Dramatic response anticipated; if not, consider other dx or ↑ dose. Consider anti-IL-6R (sarilumab, tocilizumab) > MTX to spare steroids or if relapse (*NEJM* 2023;389:1263). Follow clinical sx & ESR/CRP; relapse common.

Medium-Vessel Vasculitis

Polyarteritis nodosa ("classic" PAN) (*Arthritis Care Res* 2021;73:1061)

- **Necrotizing non-granulomatous vasculitis of medium & small arteries** (w/in muscular media) w/o glomerulonephritis or capillary involvement, not a/w ANCA
- Incidence ~5/million/y; ↑ in HBV-endemic areas; ♂ > ♀; av. age ~50. Most cases idiopathic; secondary PAN a/w **HBV** > HCV, drugs (minocycline), hairy cell leukemia.
- Clinical manifestations (*Arth Rheum* 2024;76:1120): const. sx (70%): wt loss (40%), **fever** (40%)
  Neuro (60%): **mononeuritis multiplex**, peripheral neuropathies, stroke
  Musculoskeletal (64%): **extremity pain**, **myalgias**, arthralgias, arthritis
  Renal (50%): **HTN** (30%), proteinuria, renal ischemia/infarct; *glomerulonephritis unusual*
  GI (50%): **abd pain** (20%), GIB/infarction (>10%); GU: ovarian or testicular (12%) pain
  Skin (70%): **livedo reticularis** (25%)**, ulcers** (15%), **nodules** (25%), gangrene. Small-vessel involvement: palpable purpura. Skin-limited (cutaneous PAN) not infrequent.
  Ophthalmic (10%): scleritis, retinal vasculitis, conjunctivitis, uveitis
  Cardiac (10%): coronary arteritis, cardiomyopathy (ischemic, hypertensive), pericarditis
  Pulmonary: pleural effusion (<10%); *if other lung involvement, suspect other vasculitis*
- Dx: ↑ ESR/CRP; r/o ANCA, HBV; ↓ C3/C4 if HBV-assoc.
  Angiogram (mesenteric or renal vessels) → **microaneurysms** & **focal vessel narrowing**
  CTA or **MRA** may be adequate for dx, but conventional angiogram is most sensitive
  Biopsy (nerve/muscle, deep-skin, or other affected organ) → vasculitis of medium (± small) arteries w/ fibrinoid necrosis w/o *granulomas*
  Consider ***ADA2*** gene testing for **DADA2** (PAN + strokes) as TNFi then optimal treatment
- Rx: based on severity; **steroids** + DMARD (MTX, AZA); CYC if severe; antivirals if HBV. In some, disease monophasic; consider stopping Rx if in steroid-free remission at 18 m.

ANCA-Associated Small-Vessel Vasculitis

Microvascular vasculitis (eg, capillaries, postcapillary venules, & arterioles)

Disease	Granul.	Renal	Pulm	Asthma	ANCA Type	ANCA ⊕
Granulomatosis with polyangiitis	⊕	80%	90% (+ ENT)	—	PR3 > MPO	90%
Microscopic polyangiitis	—	90%	50%	—	MPO > PR3	70%
Eosinophilic granulomatosis with polyangiitis	⊕	45%	70%	⊕	MPO >> PR3	50%

GPA is formerly Wegener's granulomatosis, EGPA is formerly Churg–Strauss. Microscopic polyangiitis (MPA).

Differential diagnosis of ANCA (*Nat Rev Dis Primers* 2020;6:71; *Lancet* 2024;403:683)

- **anti-PR3:** GPA, EGPA, microscopic polyangiitis (rarely); greater risk of relapse
- **anti-MPO:** MPA, EGPA, GPA, drug-induced vasculitis, non-vasculitic rheumatic disease
- **Atypical ANCA patterns:** drug-induced vasculitis, levamisole (cocaine contaminant, can cause dual anti-MPO/PR3), non-vasc. rheum. dis, UC, PSC, endocarditis/bacteremia, CF

Granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis)

- **Necrotizing granulomatous systemic vasculitis** frequently affecting upper respiratory tract (nose, sinuses) in addition to kidneys, lower resp tract (lungs), and other organs
- Epi: incidence 12/million/y, ↑ Northern Europe; any age but ↑ in middle-aged adults; ♂=♀
- Clinical manifestations (*Lancet Rheumatol* 2024;6:e314; *Arth Rheum* 2022;74:393)
  - Constitutional: fever, fatigue, malaise, anorexia, **weight loss**
  - **Respiratory** (90%): Upper: **recurrent sinusitis**, rhinitis, oral/nasal ulcers, epistaxis, **nasal crusting**, **saddle-nose deformity**, otitis, hearing loss, subglottic stenosis Lower: infiltrates, cavitary nodules, hemorrhage → cough, dyspnea, hemoptysis
  - **Renal** (80%): **RPGN**, microscopic hematuria (dysmorphic RBCs and casts)
  - Skin (50%): palpable purpura, livedo reticularis
  - Ocular (50%): episcleritis, scleritis, uveitis, orbital granulomas → proptosis, corneal ulcer
  - Neuro: cranial + peripheral neuropathies, **mononeuritis multiplex**
  - Heme: ↑ incidence DVT/PE when disease active
- Dx studies: **90%** ⊕ **ANCA** (80% PR3, 20% MPO), less Se in limited upper-airway disease
  - CXR or CT → nodules, infiltrates, cavities; sinus CT → sinusitis ± bone erosions
  - ↑ BUN & Cr, proteinuria, hematuria; sediment w/ RBC casts, dysmorphic RBCs
  - Biopsy → necrotizing granulomatous inflammation of arterioles, capillaries, veins. Renal bx w/ pauci-immune (minimal immune deposition) necrotizing and crescentic GN. Assess for concurrent anti-GBM disease.
- Treatment: (*Arth Rheum* 2021;73:1366)
  - **Mild disease** (no end-organ dysfxn): MTX + steroids (*Arth Rheum* 2005;52:2461)
  - **Severe disease** (end-organ damage incl. pulm hemorrhage, RPGN, etc.):
  - *Induction:* [**RTX** 375 mg/m^2/wk × 4 wk or 1 g on d1 + d15 *or* **CYC** 2 mg/kg/d PO × 3–6 mo or 15 mg/kg IV q2–3wk] + **steroids** 1 g methylpred IV × 3 d or ~1 mg/kg/d and taper (*NEJM* 2010;363:221). RTX preferred over CYC as ↓ toxicity.
  - Plasma exchange (PLEX): if concurrent anti-GBM disease; possible benefit for subset of GN at ↑↑ risk of ESRD but downsides (↑ severe infection risk) (*NEJM* 2020;382:622)
  - Adding avacopan (oral C5a receptor inhibitor) increases remission rate and allows ↓ steroids (*NEJM* 2021;384:599; *Ann Rheum Dis* 2024;83:223)
  - *Maintenance:* RTX superior to AZA if h/o relapse (*Ann Rheum Dis* 2023;82:937)
  - **Relapse:** mild → steroids ± MTX or AZA; severe → reinduce w/ steroids + RTX or CYC
  - ↑ ANCA w/o clinical evidence of flare should *not* prompt Δ Rx (*Ann Intern Med* 2007;147:611)

Microscopic polyangiitis (MPA) (*Lancet Rheumatol* 2024;6:e300)

- Similar to GPA, but **w/o ENT/upper-airway involvement & nongranulomatous**
- Epidemiology: incidence 4/million/y, ↑ Southern Europe, Asia. ♂ = ♀; avg onset 50–60 y.
- Clinical manifestations (*Arth Rheum* 2022;74:400)
  - Constitutional, neuro sx similar to GPA
  - **Renal** (80–100%): glomerulonephritis
  - **Skin** lesions (eg, palpable purpura) in 30–60%
  - **Pulmonary** (25–50%): pulmonary capillary alveolitis, **DAH**, ILD
- Dx studies: **70%** ⊕ **ANCA** (almost all anti-MPO); r/o concurrent anti-GBM disease
  - Biopsy → necrotizing **nongranulomatous** small-vessel vasculitis, pauci-immune GN
  - Cr/urinalysis (assess for GN as in GPA); CT chest if resp sx
- Treatment: as for GPA (*Arth Rheum* 2021;73:1366)

Eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg–Strauss)

- Similar to GPA w/ more frequent **cardiac involvement**, a/w **asthma** and **eosinophilia**
- Epi: rare (incidence 2/million/y); any age (typically 30–40 y); ♂ = ♀; a/w HLA-DRB4
- Clinical manifestations (*Arth Rheum* 2022;74:386)
  - Initial sx: **asthma**, sinusitis, allergic rhinitis (new asthma in adult raises suspicion)
  - Eosinophilic infiltrative disease: transient **pulm infiltrates**, gastroenteritis, or esophagitis
  - Systemic small-vessel vasculitis: **neuropathy** (mononeuritis multiplex), renal (glomerulonephritis), skin (palpable purpura, petechial, nodules)
  - **Cardiac:** coronary arteritis, myocarditis, CHF, valvular insufficiency
- Dx studies: 50% ⊕ ANCA (MPO >PR3), **eosinophilia** (>1500/μL or 10%, often >60%), biopsy → microgranulomas, fibrinoid necrosis, small artery/vein thromboses w/ eosinophilic infiltrate
- Treatment. Induction: **steroids** + mepolizumab (anti-IL-5) (if nonsevere) or RTX or CYC (if severe) (*Arth Rheum* 2021;73:1366). Relapse/refractory: add mepolizumab (anti-IL-5) or benralizumab (anti-IL-5Rα) (*NEJM* 2017;376:1921; *NEJM* 2024;390:911). Maintenance: steroid-sparing agent (DMARD or RTX) and/or anti-IL-5, low-dose steroids.

Renal-limited vasculitis

- Small-vessel pauci-immune vasculitis causing RPGN w/o other organ involvement
- Dx studies: 80% ⊕ ANCA (MPO >PR3); biopsy with pauci-immune GN ± granulomas
- Treatment identical to that for GPA/MPA

Immune Complex (IC)–Associated Small-Vessel Vasculitis

IgA vasculitis (formerly Henoch–Schönlein purpura [HSP])

- **IgA-mediated** small-vessel vasculitis w/ predilection for **skin**, **GI tract**, and **kidneys**
- Epidemiology: incidence 140/million/y; ♂ > ♀, children > adults, winter > summer
- May develop ~10 d after onset of upper resp infx or after drug exposure
- Clinical manifestations: EULAR diagnostic criteria
  - **Palpable purpura** on extensor surfaces (lower extremity first) & buttocks
  - + one of the following:
  - **Polyarthralgias/arthritis** (nondeforming) esp. involving hips, knees, & ankles
  - Colicky **abdominal pain** ± GIB or intussusception
- Nephritis ranging from **microscopic hematuria** & proteinuria to ESRD
- Dx studies: **skin bx w/ immunofluorescence → leukocytoclastic vasculitis w/ IgA** and **C3** deposition in vessel wall; renal bx → mesangial IgA deposition
- Treatment: often self-limiting over 4 wk; steroids ± DMARDs ± agents that ↓ proteinuria for renal or severe disease (*Lancet* 2023;402:859 & 2077; *NEJM* 2025;392:531 & 544)

Cryoglobulinemic vasculitis (*NEJM* 2024;391:1426)

- Cryoglobulins: immunoglobulins that **precipitate** from *serum or plasma* **in cold and redissolve on rewarming**; a/w chronic immune stimulation and/or lymphoproliferation
- Distinguish from *cryofibrinogenemia* = proteins (eg, fibrin, fibrinogen) that precipitate only from *plasma*; found in autoimmune dis, malignancies, infxns; unclear clinical significance

Types of Cryoglobulinemia			
Feature	**Type I (monoclonal)**	**Type II (mixed)**	**Type III (mixed)**
Frequency	10–15%	50–60%	25–40%
Cryoglobulin composition	*Monoclonal* Ig (usually IgG or IgM)	*Monoclonal* IgM w/ RF activity + *polyclonal* IgG	*Polyclonal* IgG and IgM
Common etiologies	**Plasma cell dyscrasias**	**Infection, malignancy**, autoimmune syndromes	**Autoimmune synd.,** infxn
Primary manifestations	**Hyperviscosity** ± thrombosis → ischemia	**IC-mediated vasculitis**, w/ multiorgan involvement. Can be asx.	

- Epidemiology: ~1/100,000, but prevalence varies with HCV rates; ♀ > ♂
- Etiologies (idiopathic in ~10%)
  - **Hematologic diseases:** multiple myeloma, MGUS, Waldenström's, chronic lymphocytic leukemia in type I; B-cell lymphomas or solid-organ malignancies in type II
  - Infxns (types II & III): viral (**HCV,** HBV, HIV, HAV, EBV, CMV), bacterial (endocarditis, strep, etc.), fungal (coccidiomycosis, etc.), parasitic (malaria, amoebiasis)
  - Autoimmune syndromes (type III > II): **Sjögren's syndrome**, SLE, RA, PAN
- Pathophysiology
  - Type I: cryo precipitation in small/med vessels → **hyperviscosity,** vascular **thrombosis**
  - Types II/III: immune complex deposition in small vessels → inflammation, complement activation → **vasculitis**
- Clinical manifestations (most Pts w/o sx)
  - Type I: **hyperviscosity** (cold worsens sx) → HA, visual Δ, livedo, digital ischemia
  - Type II/III: **vasculitis** (not affected by cold) → fever, derm (54–80%; **purpura**, livedo reticularis, ulcers), **arthralgia** (44–70%; symmetric migratory, small/med joints), **glomerulonephritis** (30–50%; MPGN), **peripheral neuropathy** (17-60%; polyneuropathy > mononeuritis multiplex), ↓ Hgb, ↓ plt, ↑ B-cell lymphoma risk, GI (5%; pain, HSM, ↑ LFTs). **"Meltzer's triad":** purpura, arthralgias, weakness in 25–30%.
- Dx studies
  - ✓ Cryoglobulins (keep blood *warmed to 37°C* en route to lab to avoid false ⊖), SPEP, SFLC. *Cryocrit* quantifies cryoprotein but not always proportional to disease activity. May see false ↑ in WBC or plt on automated CBC due to precipitation.
  - Type I: ✓ serum viscosity, typically sx if ≥4.0 centipoise; complement normal
  - Type II/III: ↓ **C4**, variable C3, ↑ ESR, ⊕ RF. ✓ **HCV, HBV, HIV**. Bx: hyaline thrombi; small-vessel leukocytoclastic vasculitis w/ mononuclear infiltrate.
- Treatment: Rx underlying disorder. Heme malig → chemoradiation; HCV → antivirals; CTD/RA → steroids + DMARD or **RTX**. Plasma exchange (± CYC) if hyperviscosity (type I) or severe/life-threatening. Cold avoidance (type I).

Connective tissue disease–associated vasculitis

- Small-vessel vasculitis a/w **RA, SLE,** or **Sjögren's syndrome**
- Clinical sx: distal arteritis (digital ischemia, livedo reticularis, palpable purpura, cutaneous ulceration); visceral arteritis (pericarditis, mesenteric ischemia); peripheral neuropathy
- Dx studies: skin/sural nerve bx, EMG, angiography; ↓ C3, C4 in SLE; ⊕ RF, anti-CCP in RA
- Treatment: steroids, cyclophosphamide, MTX (other DMARDs)

Cutaneous leukocytoclastic angiitis (*Arthritis Rheumatol* 2018;70:171)

- Most common type of vasculitis; heterogeneous group of clinical syndromes due to **IC deposition** in capillaries, venules, and arterioles; includes ***hypersensitivity vasculitis***
- Etiol: **drugs** (PCN, ASA, amphetamines, levamisole, thiazides, chemicals, immunizations, etc.); **infection** (*Strep, Staph*, endocarditis, TB, hepatitis); **malignancy** (paraneoplastic)
- Clinical manifestations: abrupt onset of **palpable purpura** and **transient arthralgias** after exposure to the offending agent; visceral involvement rare but can be severe
- Dx studies: ↑ ESR, ↓ complement levels, eosinophilia; ✓ U/A; **skin biopsy** → leukocytoclastic vasculitis ***w/o IgA deposition*** in skin (to distinguish from IgA *vasculitis*); if etiology not clear, consider ANCA, cryoglobulins, hepatitis serologies, ANA, RF
- Treatment: withdrawal of offending agent ± rapid prednisone taper

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Variable-Vessel Vasculitis

Behçet's syndrome (*NEJM* 2024;390:640)

- **Systemic vasculitis** affecting all vessel sizes, **venous and arterial**, a/w painful **oral and/or genital ulcers. Neutrophil**-rich inflammatory lesions.
- Epi: usually young adults (25–35 y); ♂ = ♀, ↑ severity in ♂; a/w HLA-B51; ↑ prev on old Silk Road (Turkey, Middle East, Asia) w/ 5 vs. 400/100,000 in U.S. vs. Turkey
- Classification criteria (#1 + ≥2 others is 91% Se & 96% Sp; *Lancet* 1990;335:1078)
  1. Recurrent **oral aphthous ulceration** (≥3× in 1 y, usually 1st manifestation)
  2. Recurrent **genital ulceration** (labia in ♀, scrotum in ♂, often scarring)
  3. **Ocular:** uveitis (esp. **panuveitis**), scleritis, retinal vasculitis, optic neuritis
  4. **Skin lesions:** pustules, papules, pseudofolliculitis, erythema nodosum
  5. ⊕ pathergy test (prick forearm w/ sterile needle → pustule) (not sensitive in Whites)
- Other clinical manifestations: most recur but are not chronic
  - Arthritis/arthralgia: nondeforming mono/oligoarticular (knees, ankles, wrists) ± enthesitis
  - Neurologic: usually involvement of midbrain parenchyma; peripheral neuropathy rare
  - Vascular: superficial or deep vein **thrombosis** (25%); arterial stenosis, occlusion, and aneurysm can also occur, including of pulmonary arteries (Hughes–Stovin syndrome)
  - Gastrointestinal: ulcers
- Dx: ↑ ESR/CRP; ulcer swab to r/o HSV; ulcer bx nonspecific; ophtho eval if sx
- Treatment (*Ann Rheum Dis* 2018;77:808)
  - Mucocutaneous: Mild: **topical steroids**, **colchicine**, dapsone, apremilast (PDE-4i) for oral & ? genital ulcers (*NEJM* 2019;381:1918). Severe: oral steroid, steroid-sparing agent.
  - Arthritis: NSAIDs, colchicine, steroids, steroid-sparing agents
  - Ocular: **topical and/or systemic steroids** ± steroid-sparing agents
  - Steroid-sparing: **anti-TNF** (*NEJM Evid* 2024;3:11), CYC, AZA, CsA, MTX, IFNα-2A
  - Venous thrombosis: steroids ± anticoagulation (careful if aneurysm present)

AUTOINFLAMMATORY SYNDROMES

Immune-mediated diseases thought to result from overactivation of innate immunity

Familial Mediterranean fever (FMF) (*Ann Rhem Dis* 2016;75:644)

- Recessive *MEFV* mutations (activating pyrin, upstream of inflammasome)
- Febrile episodes for 1–3 d w/ abd pain (serositis, can mimic acute abdomen), pleurisy, lg joint monoarthritis/arthralgia, erysipelas-like skin lesions. Variable time between attacks.
- Epi: ↑ in Armenians, Sephardic Jews, N. Africans, Turks, Arabs; onset before 10 y
- Risk of ESRD due to amyloidosis (AA), peritoneal adhesions, or infertility if untreated
- **Colchicine** effective prophylactic and ↓ amyloid; IL-1 inhibitors (*NEJM* 2018;378:1908)

TNF receptor–associated periodic syndrome (TRAPS)

- TNF receptor mutations → febrile episodes q5–6wks each lasting >7 d w/ myalgia, abd pain/nausea, migratory rash, periorbital edema; risk of amyloidosis (AA)
- Epidemiology: autosomal dom. w/ variable penetr.; prev 1/million; onset usually as child
- Rx: NSAID alone if mild flare, 7–10 d steroid course for typical flares. If freq or severe flares, **IL1 inhibitor** (*NEJM* 2018;378:1908); if refractory, TNFi (etanercept) or add colchicine.

VEXAS (vacuoles, E**1** enzyme, X-linked, autoinflammatory, somatic) **syndrome**

- Acquired mosaic *UBA*1 (ubiquitylation enzyme on X chr) mutation in HSCs → myeloid/erythroid cytoplasmic vacuoles → cytopenias, MDS, chondritis, vasculitis, thrombosis, alveolitis, neutrophilic dermatoses, fever (*NEJM* 2020;383:2628)
- Epidemiology: mostly ♂ (X-linked), mean onset age >60
- Dx: ↑ MCV, ± ↓ plts, peripheral blood somatic *UBA*1 mutation (clonal hematopoiesis)
- Steroids ↓ inflammatory manifestations but difficult to taper. Consider JAKi or IL-6i (*Ann Rheum Dis* 2024;83:1358); azacitidine, allotransplant for high-risk MDS.

Hemophagocytic lymphohistiocytosis (HLH) (*NEJM* 2025;392:584)

- ↑↑ immune activity; failure to ↓ activated macrophages by NK cells/CTLs → ↑ cytokines (IFNλ, IL-18) → macrophages phagocytize other blood cells, cytokine storm, organ failure
- Triggered by disruption of immune homeostasis: immune activation (infxn, autoimmune flare) or immunodeficiency; ~25% familial (mutations in perforin-mediated cytotoxicity)
- HLH 2/2 rheumatologic disease termed **macrophage activation syndrome** (**MAS**)
- Fever, ↑ spleen, cytopenias, ↑ TG, ↓ fibrinogen, ↑ LFTs, hemophagocytosis, ↓ NK cell activity, ↑ ferritin, ↑ soluble IL-2R; H-score for HLH likelihood (*Arthritis Rheum* 2014;66:2613)
- Rx of 1° HLH: etoposide + steroids ± CsA ± intrathecal MTX ± BMT (*Blood* 2017;130:2728). 2° HLH: Rx underlying trigger (rheum flare, infection, cancer); steroids, IL-1 inhibitor, emapalumab (anti-IFNγ), JAKi; etoposide if refractory (*NEJM* 2020;382:1811; *Ann Rheum Dis* 2023;82:1271). High mortality if no Rx.

AMYLOIDOSIS

Deposition of misfolded proteins as insoluble fibrils (β-pleated sheets) in normal tissues

Classification of Amyloidosis				
Type	**Epidem.**	**Fibril**	**Etiologies**	**Main Organs**
AL (Primary)	10/mill/y	Monoclonal Ig (light > heavy, λ>κ)	plasma cell dyscrasia (MM, MGUS, WM)	**Renal, cardiac, GI, neuro, cutaneous,** hepatic, pulmonary
AA (Secondary)	↓ cases due to Rx	Serum amyloid A (SAA)	Inflam/chr infxn: RA, IBD, FMF, osteo, TB	**Renal, GI, hepatic,** neuro, cutaneous
Hereditary ATTR	V122I in Afr Am	Mutant TTR (mTTR)	TTR mutations, most low penetrance	**Neurologic, cardiac**
Wild-type ATTR	common; ♂ >> ♀	Normal (wt) TTR	a/w aging ("senile amyloid")	**Cardiac**, aorta, GI
Aβ2M		β_2-microglobulin	Dialysis (renally cleared)	Musculoskeletal
Localized	Aβ common	β-amyloid (Aβ), Peptide horm.	Localized production and processing	Neurologic Endocrine

(*J Intern Med* 2021;289:268; *Nat Med* 2023;29:2187; *JAMA* 2024;331:778; *NEJM* 2024;390:2295)

Clinical Manifestations of Amyloidosis (*Lancet* 2016;387:2641; *JAMA* 2020;324:79)		
System	**Manifestations**	**Amyloid**
Renal	Proteinuria or nephrotic syndrome	AL, AA
Cardiac	Restrictive CMP (↓ EF late), thick walls but ↓ QRS amplitude, conduction abnl, AF, syncope	AL, mATTR, wt ATTR
GI	Diarrhea, malabsorption, protein loss; ulcers, hemorrhage, obstruction; macroglossia (dysphonia/dysphagia)	All systemic
Neuro	Periph neuropathy: painful paresthesia; carpal tunnel Autonomic neuro → impotence, dysmotility, ↓ BP; CNS (Aβ): Alzheimer's, cerebral amyloid angiopathy (CAA)	mATTR, $A\beta_2M$, AL, localized
Skin	Waxy, nonpruritic papules; periorbital ecchymoses; "pinch purpura" = skin bleeds with minimal trauma	AL
HSM	Hepatosplenomegaly w/o hepatic dysfxn or cytopenias	All systemic
Endo	Deposition with rare hormonal insufficiency	localized
MSK	Arthralgias and arthritis (especially shoulder)	AL, $A\beta_2M$
Pulm	Airway obstruction; pleural effusions	AL, AA
Heme	Factor X deficiency	AL

Diagnostic studies

- Biopsy (abd fat pad, rectal, etc.): apple-green birefring w/ **Congo red** (Se <85%, Sp >90%)
- If suspect AL: SPEP & UPEP + immunofixation, free light chains, ± BM biopsy
- If suspect renal involvement: U/A for proteinuria
- If suspect CMP: ECG (↓ volt, conduction abnl), TTE (↓ longitudinal strain, LVH, valve & septal thickening, myocard. speckling), MRI (late gad. enhancement). R/o plasma cell dyscrasia; if ⊖ → (99m)Tc-pyrophosphate (PYP) SPECT for TTR. ± Cardiac bx.
- Mass spec of biopsy to ID fibril type. Genetic testing to distinguish wt vs. hereditary ATTR.

Treatment of Amyloidosis	
AL	Limited involvement: high-dose **melphalan → auto-HSCT** (*NEJM* 2007;357:1083) Not HSCT candidate: dara-CyBorD [daratumumab + CYC + bortezomib + dexameth.] (*NEJM* 2021;385:46) Anti-amyloid Abs in development (*NEJM* 2024;390:2295)
AA	**Rx underlying disease.** Colchicine for FMF, esp. to ↓ renal dis. ? Anti-cytokine Rx (anakinra or tocilizumab) (*Clin Exp Rheumatol* 2015;33:46; *Amyloid* 2017;24:189).
ATTR	**TTR stabilizers**: tafamidis or acoramidis. ↓ **TTR production**: siRNA (patisiran, vutrisiran) or ASO (eplontersen, inotersen). ↓ neuropathy progression; ↓ CV hosp & mortality (*NEJM* 2024;390:132 & 2025;392:33). CRISPR in trials (*NEJM* 2021;385:493). Diflunisal (NSAID) slows neuropathy (*JAMA* 2013;310:2658)
$A\beta_2M$	Modify dialysis type/parameters (eg, high flux to ↑ removal), renal transplant
Aβ	Aβ antibodies (lecanemab, donanemab; *NEJM* 2023;388:9; *JAMA* 2023;330:512). Weigh CAA bleed risk with antiplatelet/anticoag. Immunosuppression (eg, steroids, CYC) for inflammatory CAA (eg, angiitis) (*J Neurol Sci* 2021;424:117425).

NEJM 2018;379:11, 22 & 1007; 2021;385:493; 2024;390:132; *Amyloid* 2023;30:1; *JAMA* 2023;330:1448

- Cardiac: diuretics; avoid CCB; ↑ dig tox (? binds amyloid); anticoag AF but bleed risk in AL
- Heart, kidney, and liver transplant may be considered in those w/ advanced disease
- Median survival: 5 y AL (~6 m if CM); 11 y AA; 4 y wt ATTR & 2.5 y *ATTR* V122I CM w/o Rx

CHANGE IN MENTAL STATUS

Consciousness/arousal (most helpful: time course and description of patient behavior)

- **Arousal:** awake → drowsy (awakens to voice) → obtunded (awakens to repeated stimuli) → stuporous (deep physical stimuli; prefer trapezius squeeze) → comatose (unarousable)
- **Coma:** lack of response to external stimuli, can use Glasgow Coma Scale. Causes: lesions in brainstem (reticular activating system), thalamus, or diffuse dysfunction in both cerebral hemispheres. Mimics: locked-in syndrome, akinetic mutism, catatonia.

Glasgow Coma Scale (sum points from each of 3 categories to calculate score)			
Eye Opening	**Best Verbal Response**	**Best Motor Response**	**Points**
		Follows commands	6
	Oriented	Localizes pain	5
Spontaneous	Confused	Withdraws from pain	4
To voice	Inappropriate words	Flexor posturing	3
To painful stimuli	Unintelligible sounds	Extensor posturing	2
None	None (intubated = 1T)	None	1

- **Delirium:** acute confusion (hrs–days), hallmark: *impaired attention*; also sleep, autonomic, hallucinations, hyper/hypoactive, especially in elderly or prior CNS injury
- **Dementia:** progressive cognitive impairment (yrs); usually affects memory, language, visuospatial, executive function, attention spared, difficult to diagnose in inpatients

Etiologies of Decreased Responsiveness	
Neurologic (*usually focal deficits*)	**Systemic** (usually *nonfocal, impaired attention*)
Vascular: ischemic stroke, ICH, VST, PRES, pituitary apoplexy Seizure: status, nonconvulsive, postictal Infection: meningitis, encephalitis, abscess Trauma: TBI, diffuse axonal injury ↑ intracranial pressure: mass, edema, hydrocephalus, herniation Inflammatory: autoimmune encephalitis, CNS vasculitis Degenerative: end-stage (eg, AD) or rapidly progressive dementia (eg, CJD)	Cardiac: global ischemia, hypo- or hypertension Pulmonary: ↓ P_aO_2, ↑ P_aCO_2 GI: liver failure, ↑ NH_3, thiamine deficiency Renal: uremia, dialysis, ↓ or ↑ Na, ↓ or ↑ Ca Heme: TTP/HUS, DIC, hyperviscosity Endo: ↓glc, DKA/HHNS, hypothyr., Addisonian ID: pneumonia, UTI, endocarditis, sepsis Hypothermia & hyperthermia Meds: anticholin. antihist., psychotrop., digoxin Toxins/withdrawal: EtOH, sedatives, opioids, CO Psychiatric: catatonia, serotonin

	syndrome, NMS

Initial evaluation

- **History** (witness & background crucial): time course, symptoms (neurologic, pain, headache, infectious, falls), PMH (eg, baseline cognition/dementia, epilepsy, cancer, cardiac, psych, infection/immune status), meds (eg, sedatives, opioids, anticholinergics, anticoag, antiseizure, immunosuppressants), drug/alcohol use
- **General exam:** VS, breathing pattern (eg, Cheyne–Stokes), tongue bite (seizure), *nuchal rigidity* (meningitis, SAH; *do not test* if possible neck trauma), ecchymoses, rash, signs of head trauma (eg, Battle sign, raccoon eyes, hemotympanum, CSF rhinorrhea), asterixis, liver disease stigmata, embolic phenomena/endocarditis, s/s drug use
- **Neuro exam** (vide infra): perform off sedatives/paralytics if possible, look for focal deficits suggesting structural cause (eg, stroke, herniation), s/s of ↑ ICP (eg, HA, vomiting, papilledema, abducens nerve palsy, unilateral dilated pupil, ↑ BP/↓ HR, fixed downgaze)

Neurologic Exam in Comatose Patients	
Mental status	Arousal (response to ↑ intensity of stimulation as above, GCS)
Cranial nerves (crucial reflexes testing brainstem function)	Pupillary reflex (II, III): *reactive to light* → normal; *pinpoint* → opioids, pontine lesion; *midposition & fixed* → midbrain lesion; *fixed & dilated* → severe anoxic injury, herniation, anticholinergic Extraocular movements/vestibulo-ocular reflex (III, IV, VI, VIII): Oculocephalic maneuver ("doll's eyes"): normal = eyes move opposite to head movement (do not test if possible neck trauma): abnormal = fixed If unable to perform (eg, cervical collar), can do vestibular (cold) caloric stimulation: normal = eyes move slowly to lavaged ear, then quickly away (*do not test w tymp memb perf*) Corneal reflex (gauze or saline), facial grimace to nasal tickle (V, VII) Gag & cough reflexes (IX, X, with ET tube manipulation if necessary)
Motor	Tone, spontaneous limb movements, best motor response (see GCS table)
Sensory	Response to painful stimuli: purposeful vs. reflexive/posturing
Reflexes	Deep tendon reflexes, Babinski, "triple" flexion (ankle, knee, & hip flexion to noxious stimulation → not suggestive of intact cortical function)

Initial treatment

- If c/f CNS infection: empiric vancomycin/CTX, consider acyclovir, ampicillin, steroids
- If c/f neck trauma: immobilization of C-spine
- Dextrose 50 g IV (with thiamine 100 mg IV to prevent Wernicke's exacerbation)
- If opioids suspected: naloxone 0.01 mg/kg; if BZD suspected, consider flumazenil 0.2 mg IV
- If concern for ↑ ICP ± herniation: ↑ head of bed; ↑ ventilation, consider osmotherapy (mannitol, hypertonic saline), dexamethasone (for tumor edema), neurosurgery

Diagnostic studies

- All patients: fingerstick glucose, electrolytes, BUN/Cr, LFTs, CBC, tox screen, U/A
- *Based on clinical suspicion:*
  - Labs: BCx, drug levels, ABG, ESR, B_{12}, HIV, ANA, NH_3, TSH, TPO/anti-TG, cort stim
  - Imaging: CT head, MRI brain; CTA head/neck if c/f stroke/SAH; XR/CT if c/f C-spine fx
  - Lumbar puncture to evaluate for meningitis, encephalitis, SAH, inflammation, ↑ ICP (usually after imaging to ensure no impending herniation from mass lesion)
  - EEG to evaluate for nonconvulsive status, seizures, toxic/metabolic encephalopathy

Treatment of delirium

- Treat underlying acute illness, eliminate precipitating factors, provide supportive care
- Improve sensory & cognitive inputs (frequent reorientation, glasses/hearing aids, etc.)
- Decrease/prevent infection and restraints, remove unnecessary lines/catheters
- Promote correct sleep/wake cycle: ensure natural sunlight, reduce nighttime light, noise, and interventions; melatonin; low-dose evening sedative med if necessary
- Meds: low-dose antipsychotics only if necessary for safety or symptom management (do not shorten delirium duration); avoid BZD except in EtOH withdrawal or seizures

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Anoxic Brain Injury (at risk if ≥5 min cerebral hypoxia)

Initial evaluation after cardiac arrest

- Neuro: arousal, command following, brainstem reflexes, motor response to noxious stimuli
- Imaging: CT usually not informative on first day, not needed prior to temperature control unless otherwise clinically indicated

Temperature control (*Intensive Care Med* 2022;48:261)

- Indications: comatose (not following verbal commands, GCS <9) after cardiac arrest from any rhythm
- No absolute contraindications to fever avoidance (if targeting hypothermia: head trauma, bleeding, surgery, hypotension are relative contraindications)
- Target should be fever avoidance (≤37.5°C) for 72 h. Some aim for hypothermia 33–36°C for 24 h if initiated immediately after ROSC, but data unclear (*NEJM* 2013;369:2197; 2019;381:2327; 2021;384:2283). Not clear 72 h superior to 36 h (*NEJM* 2023;388:888).
- Initiate as soon as possible after ROSC without delay
- Monitor core temp in bladder, place active temp management system on all Pts if available, allow passive rewarming until 37°C
- Monitor for shivering, Rx w/ acetaminophen, Mg, propofol, dexmedetomidine, or opioids
- Complications of hypothermia (if targeting 33–36°C):
  - Dysrhythmias (brady most common): if significant → rewarm
  - Hypotension: pressors, aim for MAP >65, not >70
  - Coagulopathy: monitor PT/PTT, can receive fibrinolysis, antiplatelets, anticoagulants
  - Infection: surveillance urine, sputum and blood cultures every 12 h
  - Hyperglycemia during cooling, hypoglycemia w/ rewarming
  - Hypokalemia during cooling, hyperkalemia w/ rewarming

Ongoing evaluation

- Neuro exam: daily coma exam. Not reliable in 1st 24 h or on sedation. Should be off all sedation for adequate time (depends on dose, duration, metabolism).
- Labs: daily CBC, PT/PTT, electrolytes. Serum neuron-specific enolase (NSE) on days 1–3.
- Imaging: head CT 24 h after arrest; if unrevealing, consider MRI around days 3–5
- EEG: recommended in all to exclude seizures; greatest risk during rewarming. Unreactive background or abundant rhythmic or episodic discharges may convey poor prognosis.
- Somatosensory evoked potentials (SSEP): electrical responses in CNS to somatosensory stimulation; consider for prognosis 48–72 h after rewarming

Prognosis (*Neurocrit Care* 2023;38:533)

- Neuroprognostication of what functional status will be 3 mo after cardiac arrest challenging
- Defer assessment for 72 h after ROSC (or after rewarming), avoid sedation, use multimodal assessment, observe for longer if within GoC

- Predictors of poor outcome (48–72 hrs after arrest or rewarming): no pupillary response, absent SSEP, CT with diffuse loss of gray-white differentiation with sulcal effacement, MRI with diffuse diffusion restriction, EEG suppressed. *Unreliable* predictors: age, rhythm, and time to ROSC.

SEIZURES

Definitions & clinical manifestations (*Epilepsia* 2017;58:522)

- **Seizure:** transient neurologic symptoms due to excessive synchronous neuronal activity; may be *provoked* by a reversible factor lowering the seizure threshold, or *unprovoked*
- **Epilepsy:** ≥2 unprovoked seizures occurring >24 h apart *or* 1 unprovoked seizure w/ ≥60% probability of further seizures over the next 10 y (vide infra for prognostication)
- **Generalized seizures** (involves brain diffusely since onset)
  - *Tonic-clonic* (grand mal):
    - **Aura** (sec to mins): premonition with paresthesias, focal motor contractions, abnormal smells/tastes, fear, depersonalization, déjà vu, autonomic changes, automatisms
    - **Ictal period** (sec to mins): possible gaze and head deviation, tonic contraction of muscles → intermittent relaxing and tensing of muscles, tongue biting, urinary incontinence, pooling of secretions
    - **Postictal period** (mins to h): slowly resolving period of confusion, disorientation, and lethargy. May be accompanied by focal neurologic deficits (Todd's paralysis).
  - *Absence* (petit mal): lapse of consciousness × sec w/o loss of postural tone, pediatric dx
  - *Myoclonic* (infantile spasms & juvenile myoclonic epilepsy): sudden, brief contraction
- **Focal seizures** (involves discrete brain area, often associated with a structural lesion)
  - *w/o impaired awareness:* focal motor/autonomic sx (formerly "simple partial seizure") or focal sensory/psychic symptoms (eg, aura)
  - *w/ impaired awareness:* lasts mins w/ dyscognitive features (formerly "complex partial seizure") and postictal state
  - *evolving to bilateral, convulsive seizure* (formerly "secondarily generalized seizure")
- **Status epilepticus:** continuous convulsive seizure ≥5 min or >2 seizures w/o resolution of postictal encephalopathy; *life threatening*
- **Nonconvulsive status epilepticus:** alteration of awareness (ranging from confusion to coma) w/o motor manifestations of seizure; dx with EEG

Differential Diagnosis

Feature	Seizure	Psychogenic Non-epileptic Seizures (PNES)	Syncope
Aura	Unusual behavior/automatisms	Unusual; crying/talking during event	Diaphoresis, nausea, tunnel vision
Convulsions	Variable duration	Variable duration	Usually <10 sec
Postictal state	Yes; can be ≥30 min	Typically none	None or short
Other clues	Tongue biting, incontinence	Irregular shaking, response to voice or touch	Skin pallor, clamminess
Other: metabolic disorders (eg, alcoholic blackouts, hypoglycemia), migraine, TIA, transient global amnesia, narcolepsy (cataplexy), nonepileptic myoclonus, tics, asterixis			

Etiologies of seizures (vary strongly by age)

- **Without focal lesion:** genetic predisposition to seizures or epilepsy syndrome; alcohol withdrawal, illicit drugs; meds (eg, β-lactams, bupropion, fluoroquinolones, tramadol, MNZ, meperidine, CsA); electrolyte (hyponatremia) & other metabolic (eg, uremia, liver failure, hypoglycemia); autoimmune encephalitis, idiopathic (~60%)
- **With focal lesion:** tumor, trauma, stroke, subdural hematomas, posterior reversible encephalopathy syndrome, mesial temporal sclerosis, abscess, focal cortical dysplasia

Clinical evaluation (*JAMA* 2016;316:2657)

- *History key in differentiating seizure from other causes of transient loss of consciousness*. Must talk to witnesses. Ask about prodrome, unusual behavior before spell, type & pattern of abnl movements incl. head turning & eye deviation (gaze preference usually *away* from seizure focus), incontinence, loss of responsiveness, postictal.
- Recent events: illnesses/fevers, head trauma, sleep deprivation, stressors
- PMH: prior seizures or ⊕ FHx; prior CNS infection, stroke, or head trauma; dementia
- Medications (new or noncompliance), alcohol and illicit drug use
- General physical exam should include skin color changes (pallor, cyanosis, bruises), lateral tongue bite, and transient focal weakness suggestive of Todd paralysis
- Neurologic exam should look for focal abnormalities → underlying structural abnormality

Diagnostic studies (*Neurology* 2007;69:1996)

- Lab: full lytes, BUN, Cr, glc, LFTs, CK, lactate, tox screen, AED levels (to evaluate for noncompliance or insufficient dose), illicit drug screen
- Routine EEG (~30 min): may help determine risk of seizure recurrence after 1st-time unprovoked seizure. OutPt if full recovery. Caveat: interictal EEG nl in 50% of Pts w/ epilepsy, and interictal epileptiform activity (spikes or sharp waves) seen in up to 2% of nl population; EEG w/in 24 h, sleep deprivation and repeated studies ↑ dx yield of EEG.
- Long-term EEG monitoring (hrs to days): if suspicion for nonconvulsive status or non- epileptic seizures; video monitoring may help w/ nonepileptic seizures (spell capture)
- MRI to r/o structural abnormalities; ↑ Se w/ fine coronal imaging of frontal & temporal lobes
- Head CT scan: urgent CT scan if neuro deficits, headache, fever, cognitive change, trauma
- LP (if no space-occupying lesion on imaging): if suspect meningoencephalitis (eg, fever, ↑ WBC, nuchal rigidity), autoimmune encephalitis, and in *all* HIV ⊕ Pts

Treatment (*Neurology* 2015;84:1705; *Lancet* 2015;385:884)

- Treat any underlying precipitants, including CNS infections, intoxication, withdrawal, discontinuing provoking med, etc.
- Antiepileptic drug (AED) Rx usually reserved for Pts w/ ≥2 *unprovoked* seizures, single seizure w/ high risk of recurrence (vide infra), or underlying structural abnormality. *Provoked* seizures usually generalized, treated by addressing underlying cause; consider AED if status epilepticus on presentation, focal neuro exam, postictal Todd's paralysis.
- After 1st unprovoked sz, weigh risks of recurrence vs. AED. ↑ risk of recurrence if abnl EEG, MRI, or nocturnal sz. If EEG & MRI nl → 65% sz-free at 5 y (*Lancet Neurol* 2006;5:317).
- Immediate treatment w/ AED after 1st unprovoked seizure ↓ risk of recurrence over 2 y, but does not Δ long-term prognosis. Introduce gradually, monitor carefully.
- If AED Rx indicated, choice dependent on type of seizure, side effects, cost, mechanism of elimination (if hepatic or renal insufficiency), teratogenesis, and drug interactions
- Individual state laws mandate seizure-free duration before being allowed to drive

Antiepileptic Drugs and Side Effects (*Continuum* 2022;28:500)

Medication	Avg Daily Dose	Common Side Effects	
		Systemic	*Neurologic*

			(all: sedation)
Brivaracetam	100–150 mg	GI upset (rare)	Dizziness
Carbamazepine	400–1600 mg	Aplastic anemia, ↓ WBC, rash, hepatotoxicity, ↓ Na	Diplopia, confusion, ataxia
Cenobamate	200–350 mg	Rash, DRESS, SI	Cog slowing, coord. & visual Δs
Clobazam	20–40 mg	Constipation	Nystagmus, incoord.
Ethosuximide	500–1500 mg	Rash, BM suppression	Behavioral Δs
Gabapentin	900–3600 mg	GI upset, wt gain	Nystagmus, ataxia
Lacosamide	200–400 mg	Prolonged PR interval	Dizziness, diplopia
Lamotrigine	100–300 mg	Rash (Stevens–Johnson)	Tremor, HA, blurred vision, insomnia
Levetiracetam	1000–3000 mg	GI upset (rare)	Emotional lability
Oxcarbazepine	600–2400 mg	Hyponatremia, rash	Diplopia, dizziness
Perampanel	4–8 mg	GI upset, weight gain	HA, ataxia, visual and behavioral Δs
Phenobarbital	50–200 mg	Rash	Cognitive slowing
Phenytoin	200–400 mg	Gum hyperplasia	Dizziness, ataxia
Topiramate	100–400 mg	↓ wt, hypohidrosis, kidney stones, glaucoma, met acid	Cognitive slowing
Valproic acid	500–2500 mg	Hepatotox, ↑ NH_3, ↑ wt, ↓ hair	Tremor
Zonisamide	200–600 mg	↓ wt, hypohidrosis, nephrolith	Cog slowing, fatigue

Status epilepticus (*Epilepsy Curr* 2016;16:48; *Continuum* 2022;28:559)

- ABCs: vital signs, oral airway or endotracheal intubation. Place Pt in semiprone position to ↓ risk of aspiration. Obtain IV access. Give thiamine, dextrose, IV normal saline.
- STAT POC glc, metabolic panel, CBC, tox screen, CK, lactate, AED levels, ± head CT, LP
- Start standing AED after loading dose

Treatment of Status Epilepticus			
Time (min)	**Antiepileptic**	**Dosing Regimen**	**Typical Adult Dose**
5–20	**Lorazepam** or **Midazolam** or **Diazepam**	0.1 mg/kg IV>IM 0.2 mg/kg IM 0.2 mg/kg IV or 0.2–0.5	2–4 mg IV pushes, up to 8 mg Up to 10 mg ×1

		mg/kg PR	Up to 10 mg IV; up to 20 mg PR
20–40	**Phenytoin** or **Fosphenytoin** or **Valproate** or **Levetiracetam**	20 mg/kg 20 mg PE/kg 40 mg/kg 60 mg/kg	1.0–1.5 g IV (max 1.5 g) over 20 min 1.0–1.5 g PE IV over 5–10 min 1.0–1.5 g IV (max 3 g) over 5–10 min 4 g IV (max 4.5 g) over 10–15 min
	Subsequent steps mandate intubation, EEG monitoring, and ICU admission		
40–60	General anesthesia with continuous midazolam, pentobarbital, or propofol		

ALCOHOL WITHDRAWAL

Clinical manifestations

- Minor withdrawal: 6–48 h after last drink; mild anxiety, tremulousness, diaphoresis, HA
- **Withdrawal seizures:** typically w/in 48 h after last drink; if unRx'd, 1/3 → delirium tremens
- **Alcoholic hallucinosis:** isolated hallucinations (typically visual) 12–48 h after last drink
- **Delirium tremens** (**DT**): disorientation, agitation, hallucinations, ↑ HR & BP, fever, diaphoresis; begins 48–96 h after last drink, lasts 5–7 d
- Consider: infxn, meningoencephalitis, bleed, sz, drug O/D, coingestions, ALF, GIB
- Ten-item scale (CIWA-Ar) used to assess and manage alcohol withdrawal (see Appendix)
- Wernicke's encephalopathy (WE): thiamine defic → ophthalmoplegia, gait ataxia, confusion

Treatment (*J Addict Med* 2020;14:1)

- **Benzodiazepines**:
  - Drug: diazepam preferred (long-acting; ↓ risk of recurrent withdrawal), lorazepam (short-acting), chlordiazepoxide, oxazepam (no active metab; good if cirrhosis)
  - Dosing: typically start w/ diazepam 10–15 mg IV q10–15min (or lorazepam 2–4 mg IV q15–20min) until appropriate sedation achieved, then titrate to CIWA-Ar scale, evaluating q1–4h until score <10 × 24 h, then q4–8h × 24 h, and if stable, then q4h
- **Phenobarbital:** adjunctive use in severe withdrawal, Pts with refractory DTs
- *Avoid* βB (mask sx)
- Mechanical restraints as needed until chemical sedation achieved
- Volume resuscitation as needed; replete K, Mg, PO_4
- Thiamine: 200 mg IV daily × 3 d for ppx; if suspect WE → 500 mg IV tid × 2 d (& prior to glc)
- Ppx: if min sx or asx (ie, CIWA score <8) but prolonged heavy EtOH consumption or h/o withdrawal seizures or DTs → chlordiazepoxide 25–100 mg q6h × 24 h, then taper

DIZZINESS

Differential diagnosis

- Includes a variety of sx. **Disequilibrium:** sense of imbalance, gait disturbance; **vertigo:** perception of movement; **near syncope:** lightheadedness due to cerebral hypoperfusion.
- Dizziness can occur with PNS & CNS injury (vide infra) or in hematologic (eg, anemia), CV (eg, arrhythmia, orthostasis), & endocrine (eg, ↓ glc, thyroid) disorders, or due to meds
- Vertigo Ddx:
  Peripheral (inner ear/CN VIII)
    BPPV: dislodged canaliths in semicircular canal; episodic rotatory vertigo (<1 min episodes), triggered by changes in position; Rx: Epley/BBQ roll maneuver
    Ménière's disease: ↑ endolymphatic pressure in inner ear; episodic rotatory vertigo (min–hrs), N/V, aural fullness, hearing loss, tinnitus; Rx: diuretics, ↓ salt
    Vestibular neuritis: sudden-onset w/ gait ataxia; severe for 24–48 hrs followed by gradual improvement, often postviral; w/ hearing loss = labyrinthitis; Rx = PT
  Central (brainstem/cerebellum)
    Posterior circulation stroke/TIA: "5 Ds" of dizziness, diplopia, dysarthria, dysphagia, dystaxia; sudden onset (resolves after mins in TIA, persists in stroke)
    Other: migraine, Chiari, epilepsy, MS, tumors, drugs/meds, concussion

Initial evaluation

- **Hx:** ask open-ended questions (description by Pt may be unreliable), pace of illness, episodic vs. chronic, meds, other sx of posterior circ including diplopia, dysarthria, ataxia

Exam	Peripheral Causes	Central Causes
Orthostatics	⊕ in orthostatic syncope	Typically absent
Eye movements	Nystagmus unidirectional if present, never vertical, suppressed w/ fixation	Nystagmus bidirectional, often vertical, not suppressed w/ fixation
Hearing	May be impaired in some peripheral causes of vertigo	Normal (rarely unilat. hearing loss in AICA territory stroke)
Coord./gait	Normal	May reveal limb, trunk, gait ataxia

- **HINTS testing** (*Stroke* 2009;40:3504): only performed in the acutely dizzy Pt
  Head **I**mpulse test: Pt fixates on examiner's nose during rapid passive head turn of ~10–20°; presence of "catch-up saccade" supports peripheral dysfunction to side of turn
  Nystagmus (see table above)
  Test of **S**kew: vertical refixation saccade on alternating eye cover supports central cause
- **Dix–Hallpike test:** Pt sitting → lying back w/ 45º head tilt; elicits rotatory nystagmus after delay of secs; fatigues if repeated; ⊕ suggests BPPV w/ affected ear down
- **Supine Roll test:** nystagmus elicited by head turn while patient supine; when ⊕ suggests BPPV w/ affected ear down (lateral canal, 8% of cases)
- **Studies:** orthostatic VS, basic labs, ECG; if concerning s/s HINTS → MRI brain
- **Rx:** Epley for BPP; vestib. PT; anti-hist., sedative or anti-emetic, steroid for vestib. neuritis

STROKE

Ischemic Stroke

Etiologies

- Embolic: atheroembolic, cardioembolic (~30% due to AF; *NEJM* 2014;370:2478), paradoxical

- Thrombotic: large vessel (atherosclerosis) vs. small vessel ("lacunar", lipohyalinosis of small arteries, often related to smoking, HTN, hyperlipidemia, & DM)
- Other: hypoperfusion, dissection, vasculopathy (vasculitis, radiation), vasospasm, hypercoag, hematologic (sickle cell, hyperviscosity), endocarditis, venous

Clinical manifestations

- Timing: embolic → sudden onset; thrombotic → may have stuttering course

Stroke Syndromes by Vascular Territory	
Artery	**Deficits**
ICA → Ophth	Amaurosis fugax (transient monocular blindness)
ACA	Hemiplegia (leg > arm), abulia, urinary incontinence, primitive reflexes
MCA	Hemiplegia (face & arm >leg); hemianesthesia; homonymous hemianopia Aphasia if dom. hemisphere: sup. div. → expressive; inf. div → receptive Apraxia & neglect if nondom. hemisphere
PCA	Macular-sparing homonymous hemianopia; alexia w/o agraphia Thalamic syndromes with contralateral hemisensory disturbance
Vertebral, PICA	Wallenberg syndrome = numbness of ipsilateral face and contralateral limbs, diplopia, dysarthria, dysphagia, ipsilateral Horner's, hiccups
Basilar	Pupillary Δs (midbrain=dilated, pons=pinpoint), long tract signs (quadriplegia, sensory loss), CN abnl, cerebellar dysfxn. Top of basilar → "locked-in" synd.
Cerebellar	Vertigo, N/V, diplopia, dysarthria, nystagmus, ipsilateral limb ataxia
Lacunar (arterioles)	5 major syndromes: pure hemiplegia, pure hemianesthesia, ataxic hemiparesis, dysarthria + clumsy hand, mixed sensorimotor

Transient ischemic attack (TIA)

- Sudden deficit due to cerebral ischemia; **no stroke on imaging;** most resolve in <1 h
- Ddx: seizure, migraine, hypoglycemia, transient focal neurologic episodes, TGA, anxiety
- Risk of stroke ~2% by 1 wk (*NEJM* 2016;374:1533 ; *JAMA* 2025;333:1508). Can stratify based on **ABCD^2:** **A**ge ≥60 y (+1); **B**P ≥140/90 (+1); **C**lin features: unilat. weak. (+2), speech impair. w/o weakness (+1); **D**uration ≥60 (+2) or 10–59 min (+1); **D**M (+1).

Physical exam

- General: murmurs, carotid & subclavian bruits, peripheral emboli, endocarditis stigmata
- Neurologic exam, NIH stroke scale (https://www.ninds.nih.gov/sites/default/files/2024-05/KnowStroke_NIHStrokeScale_May2024_508c.pdf)

Acute workup

- Electrolytes, Cr (relevant for contrast); glc, CBC, coags (see exclusion criteria for lysis)
- Cardiac biomarkers, 12-lead ECG, tox screen
- **STAT CT head and CTA head & neck** to evaluate for established infarct, r/o ICH prior to lysis, and evaluate for possible endovascular Rx. Early signs of stroke: hyperdense artery, loss of gray-white differentiation, edema, insular ribbon. CT can be nl initially, & not Se for small or brainstem stroke.

Acute treatment of ischemic stroke (*Stroke* 2019;50:e344; *JAMA* 2021;325:1088)

- **Thrombolysis (IV):** tPA 0.9 mg/kg (max 90 mg), w/ 10% as bolus over 1 min, rest over 1 h
  consider if onset w/in 4.5 h, Ø contraindic. (incl. current/prior ICH; head trauma or stroke w/in 3 mo; intracranial neoplasm, AVM or aneurysm; recent intracranial/intraspinal surgery; active internal bleeding; noncompressible arterial puncture; ↑ BP; multilobar infarct; plt <100k, INR >1.7, on Xa inhib, PTT >40, glc <50)
  0–3 h: 12% absolute ↑ in good neuro outcome (min/no disability), 5.8% absolute ↑ in ICH, trend toward 4% absolute ↓ mortality
  3–4.5 h: 7.4% absolute ↑ in good neuro outcome, 1.8% absolute ↑ in ICH, Ø mortality benefit (nb, trial excluded patients with previous strokes + DM)
  Tenecteplase (TNK) IV bolus only 0.25 mg/kg (max 25 mg) is noninferior alternative and may be preferred if Pt eligible to undergo mechanical thrombectomy (*Stroke* 2019;50:12)
- **Endovascular thrombectomy** if w/in 6 h of sx onset, pre-mRS 0-1, occlusion in ICA or MCA, NIHSS ≥6, ASPECTS ≥6 (CT-based likelihood of recovery). May extend to 6–24 h if mismatch between infarct size & clinical deficits or stroke penumbra (*NEJM* 2022;386:1359).
- BP: lower to <185/110 to consider lysis; if lyse keep <180/105 × 24 h (consider IV labetalol or nicardipine), o/w permissive HTN unless >220/120 or sx; if sx HoTN consider vasopressors
- Initiate ASA w/in 24–48 h; avoid anticoagulation w/in 24 h of lysis; vide infra for long-term Rx
- Cerebral edema → herniation: 1–5 d post-large MCA or cerebellar strokes, ↑ risk in young. Elevate HOB >30°; mannitol ±23% NaCl. Hemicraniectomy ↓ mortality (*NEJM* 2014;370:1091). Neurosurgery consult in select MCA and all large cerebellar strokes.

Workup to assess for etiology/modifiable risk factors

- Cardiac: monitor for AF (inPt and extended outPt); TTE to r/o thrombus/veg, w/ bubble study to r/o PFO/atrial septal aneurysm if suspect embolic and Pt young
- Vessel imaging: CTA or MRA head/neck; carotid U/S w/ Doppler if CTA/MRA contraindic.
- Labs: lipids, Hb_{A1C}, TSH, homocysteine, Lp(a), hypercoag w/u (if <65 y or cryptogenic stroke; ideally drawn before starting anticoag), ESR/CRP, blood cx if s/s systemic infection
- **MRI** helpful if dx of stroke unclear (esp. post circ) or to define stroke subtype, age, size
  DWI bright/*ADC* dark = earliest finding in acute ischemia (~w/in mins, up to days)
  T2-FLAIR: hyperintense w/in about 6 hrs, persists for wks

Secondary stroke prevention (*Stroke* 2021;52:e364)

- **Antiplatelet therapy:** different agents likely have similar efficacy
  ASA ↓ death & repeat stroke; equal to warfarin in nonembolic stroke (*NEJM* 2001;345:1444)
  clopidogrel: marginally superior to ASA, slightly ↑ ICH (*Lancet* 1996;348:1329)
  $P2Y_{12}$ (clopi or ticag) + **ASA** (vs. ASA alone): Rx for 1–3 mos in *minor* strokes or TIA w/ high $ABCD^2$ → ↓ risk of ischemic stroke, ↑ ICH (*NEJM* 2018;379:215; 2020;383:207; 2023;389:2413). Rx for 90 d if stroke due to intracranial athero (*NEJM* 2011;365:993).
- **Anticoagulation (AC):** consider for AF (qv), cardiac/paradoxical emboli (except bacterial endocarditis); large extradural dissections; hypercoag; bridge to CEA in sx carotid stenosis. Timing depends on stroke size: minor/moderate = <48 h; major = 1–2 wks or even w/in 4 d if using DOAC and w/o hemorrhage (*NEJM* 2023;388:2411; *Lancet* 2024;404:1731).
- Long term: SBP target <130/80 mmHg, LDL-C <70 mg/dL (*NEJM* 2017;376:1713)
- **Carotid revascularization** (*NEJM* 2013;369:1143)
  CEA (*if* surgical morbidity & mortality ≤6%) indicated for:
    sx stenosis 70–99% (benefit ↑ for males, >75 y, ≤2 wk from stroke) → 65% ↓ RR of repeat stroke, slight benefit for 50–69% stenosis (*NEJM* 1991;325:445; *Lancet* 2004;363:915)
    asx stenosis 70–90%, <79 y: 50% ↓ RR of repeat stroke (*Lancet* 2010;376:1074), although incidence of stroke in asx Pts in modern era <1%/y (*JAMA* 2022;327:1974)
  Stenting: c/w CEA, ↑ periprocedural stroke (esp. in elderly) & ↓ MI (but many asx); subseq. ≈ rates of fatal or disabling stroke, but ↑ nondisabling stroke (*Lancet* 2021;398:1065)

Patent foramen ovale (PFO; in ~25% of population) (*NEJM* 2005;353:2361)

- ↑ stroke risk: ≥4 mm separation, R → L shunting at rest, ↑ septal mobility, atrial septal aneurysm
- Risk scores assess likelihood stroke related to PFO. RoPE score: age (+1 for each decade <70); cortical stroke on imaging (+1); HTN, DM, h/o stroke/TIA, smoker (+1 for each *absent* risk factor). PASCAL classification also includes large shunt or atrial septal aneurysm.
- If PFO & stroke/TIA: no benefit of warfarin vs. ASA; consider if high risk for or has DVT/PE
- Closure ↓ recurrence by ≥50%, with magnitude of benefit dependent on risk classification (RoPE ≥7 or PASCAL classification of possible or probable) (*JAMA* 2021;326:2277)

Intracranial Hemorrhage (ICH)

Classification by location

- Hemorrhagic strokes: intraparenchymal hemorrhage (IPH) & subarachnoid hemorrhage (SAH)
- Other ICH: epidural hematoma (EDH) & subdural hematoma (SDH)

Etiologies

- AVM, aneurysm, cerebral venous sinus thrombosis → IPH or SAH
- HTN (basal ganglia, cerebellum, brainstem), cerebral amyloid (lobar), tumor (esp. w/ melanoma, renal cell CA, chorio-CA, thyroid CA) → IPH
- Trauma → all locations (nb, IPH or SAH caused by trauma technically not a stroke)

Clinical manifestations (*Lancet* 2017;389:655 *& NEJM* 2017;377:257)

- ↓ consciousness, N/V, HA, progressive focal neurologic deficits, seizure
- *SAH:* thunderclap HA, onset w/ exertion; nuchal pain/rigidity; LOC. *EDH:* initial lucid interval.

Workup (*Acad Emerg Med* 2016;23:963)

- **STAT CT brain, angio (CT-A or conventional) if suspicious for vascular source**
- Coags (PT, PTT, INR)

Management (*Crit Care Med* 2016;44:2251; *JAMA* 2019;321:1295)

- Reverse coagulopathy, INR <1.4. Plt >100k, no need for plt tfn if on antiplt Rx (? if ↑ ICH), DDAVP if uremic. 2–3 mo later can restart antiplt mono Rx (*Lancet* 2019;393:2013).
- BP control w/ art line, nicardipine or labetalol gtt. SBP goal <140 for 1st 24 h, then <160 (*NEJM* 2013;368:2355 & 2016;375:1033), though BP goals controversial (*NEJM* 2016;375:1033).
- SAH: endovasc coiling vs. surg clipping (depends on location, comorbid.; *Lancet* 2015;385:691) of aneurysm/AVM; nimodipine to ↓ risk of vasospasm (monitor w/ TCDs), seizure Ppx
- Surg evac: EDH; SDH if >1 cm or rapid ↑, Rx-resistant epilepsy; IPH: no obvious benefit
- Venous sinus thrombosis: start anticoagulation, manage ↑ ICP and seizures as needed

WEAKNESS & NEUROMUSCULAR DYSFUNCTION

Feature	Upper Motor Neuron	Lower Motor Neuron	Neuromuscular Junction	Myopathy
Distribution of weakness	UE Ext, LE Flex, hip abductors	Distal, segmental	Ocular, bulbar, proximal limb	Proximal, symmetric
Atrophy	None	Severe	None	Mild
Fasciculations	None	Common	None	None
Tone	↑	↓	Normal	Normal or ↓
Reflexes (DTRs)	↑	↓	Normal	Normal or ↓
Toes (Babinski)	Upgoing	Downgoing	Downgoing	Downgoing

Peripheral Neuropathies

Etiologies based on presentation

- **Mononeuropathy** (1 nerve): *acute* → trauma; *chronic* → entrapment, compression, DM, Lyme. Common: median nerve (carpal tunnel); ulnar (elbow or wrist); radial (spiral groove); com. peroneal (fibular head w/ leg crossing); lat. femoral cutan. (inguinal lig).
- **Mononeuropathy multiplex** (axonal loss of multiple, noncontig. nerves): vasculitis. (eg, PAN, EGPA, GPA, SLE, RA, Sjögren's, cryo, HCV), DM, Lyme, HIV, leprosy, hereditary neurop. w/ pressure palsies, infiltrative (sarcoid, lymphoma, leukemia)
- **Polyneuropathy** (multiple symmetric nerves, generally length dependent): 30% idiopathic
  - *W/ autonomic features:* DM, EtOH, paraneoplastic, B_{12} def, amyloid, chemo, 1° dysauto
  - *Painful (small fiber nerves):* DM, EtOH, amyloid, chemo, sarcoid, heavy metals, porphyria
  - *Demyelinating.* Acute: AIDP (Guillain–Barré), diphtheria. Subacute: meds (taxanes), paraneoplastic. Chronic: idiopathic, DM, CIDP, anti-MAG, HIV, hypothyroidism, toxins, paraproteinemia, hereditary (eg, CMT).
  - *Axonal.* Acute: acute motor axonal neuropathy, porphyria, vasculitis, uremia, critical illness. Subacute: EtOH, sepsis, paraneoplastic, meds (cisplatin, paclitaxel, vincristine, INH, ddI, amio). Chronic: DM, uremia, lead, arsenic, HIV, paraproteinemia, B_{12} defic.

Clinical manifestations

- Weakness, fasciculations, cramps, numbness, dysesthesias (burning/tingling), allodynia
- ± Autonomic dysfxn (orthostasis, constipation, urinary retention, impotence, abnl sweating)
- Depressed or absent DTRs (may be normal in small fiber neuropathy)

Diagnostic studies

- Distal symmetric polyneuropathy: CBC, lytes, BUN/Cr, Hb_{A1C}, B_{12}, ESR, SPEP + IF
- EMG/NCS (often no change in 1st 10–14 d or in small fiber neuropathy)
- Based on H&P: LFTs, celiac Abs, ANA, anti-Ro/La, HIV, Cu, Lyme, RPR, UA, UPEP+IF, ACE, ANCA, heavy metals, LP (AIDP/CIDP), cryo, paraneoplastic Abs, genetics. Auto-nomic testing/skin bx (small fiber), nerve bx (mononeuro. multiplex), fat pad bx (amyloid).
- MRI if possible radiculopathy or plexopathy (after EMG)

Pharmacologic treatment of neuropathic pain (*Lancet Neurol* 2015;14:162)

- Gabapentin, pregabalin, TCAs (nortriptyline, amitriptyline), SNRIs (duloxetine, venlafaxine)
- 2nd line: tramadol, topicals (lido, capsaicin); 3rd line: nerve block, botulinum toxin A

Guillain–Barré Syndrome (GBS)

Definition & epidemiology (*Lancet* 2021;397:1214)

- AIDP (60–80%); acute motor axonal neuropathy (AMAN; 7–30%; a/w anti-GM1, anti-GD1a Abs; worse prognosis); Miller Fisher synd. (ophthalmoplegia & ataxia; a/w anti-GQ1b Ab)
- Incidence 1–2 per 100,000; most common acute/subacute paralysis
- Precipitants in 60%: viral illness (influenza, CMV, EBV, HIV, Zika, COVID-19), URI (*Mycoplasma*), gastroenteritis (*Campylobacter*), Lyme, immunizations, immune checkpoint inhibitors, surgery

Clinical manifestations (*Nat Rev Neurol* 2019;15:671)

- Pain (55–90%), distal sensory dysesthesias & numbness often 1st sx, back pain common
- Progressive symmetric paralysis in legs and arms over hrs to days; plateau in 1–4 wk
- Hypoactive then absent reflexes. <10% w/ reflexes on presentation, but all develop hypo/areflexia during course. Minority of AMAN w/ preserved reflexes throughout.
- Resp failure requiring mech vent occurs in 25%; autonomic instability & arrhythmias in 60%

Diagnostic studies (results may be normal in first several days)

- LP: albuminocytologic dissociation = ↑ protein w/o pleocytosis (<10 WBCs) seen in up to 64% of Pts. ↑ protein in ½ in 1st wk, ¾ by 3rd wk of sx. Unlikely to be GBS if WBC >50.
- EMG/NCS: ↓ conduction velocity, conduction block, abnl F-waves; can be nl in 1st 2 wk
- FVC & NIF: to assess for risk of resp. failure (cannot rely on P_aO_2 or S_aO_2 alone)

Treatment

- **Plasma exchange or IVIg of equal efficacy** (*Neuro* 2012;78:1009); steroids not beneficial
- Supportive care with monitoring in ICU setting if rapid progression or resp. failure
- Watch for autonomic dysfunction: labile BP, dysrhythmias, urinary retention, ileus
- Erasmus GBS outcome score can help w/ prognostication (*Lancet Neurol* 2007;6:589). Most recover near baseline in 1 y; 3–5% mortality. Residual deficits: pain, fatigue.

Myasthenia Gravis (MG)

Definition & epidemiology (*Lancet Neurol* 2015;14:1023; *NEJM* 2016;375:2570)

- Autoimmune disorder with Ab against acetylcholine receptor (AChR, 80%), muscle-specific kinase (MusK, 4%), lipoprotein-related protein 4 (LRP4, 2%), or other NMJ proteins
- Prevalence: 150–250 per million; all ages, peak incidence 20s–30s (F), 60s–70s (M)
- 15% of AChR MG a/w thymoma; 30% of Pts w/ thymoma develop AChR MG

Clinical manifestations

- Fluctuating weakness w/ *fatigability* (worse w/ repetitive use, relieved by rest)
- Cranial muscles involved early → 60% present initially w/ ocular sx (ptosis, diplopia); 15% confined to ocular sx; 15% w/ bulbar (difficulty chewing, dysarthria, dysphagia)
- Limb weakness proximal > distal; DTRs preserved; minimal/no atrophy
- MusK MG (F >> M): more severe limb/facial/bulbar weakness, muscle atrophy
- Exacerb. triggers: URI, surgery, preg/postpartum, meds (eg, Mg, AG, macrolides, FQ, procainamide, phenytoin, D-penicillamine, β-blocker). Prednisone can *worsen* sx acutely.
- Myasthenic crisis = sx exacerbation, risk of respiratory compromise
- Cholinergic crisis = excessive Rx with anticholinesterases: salivation, cramping, diarrhea

Diagnostic studies

- Bedside: ptosis, worse after >45 sec of sustained upgaze; improved with ice pack over eyes for 2–5 min (Se 77%, Sp 98%), ophthalmoplegia, weakness
- EMG: ↓ response with repetitive nerve stimulation (vs. ↑ response in Lambert–Eaton)
- Anti-AChR binding Ab (Se 80%, 50% if ocular disease only, Sp >90%); muscle-specific receptor tyrosine kinase (MusK) Ab
- CT or MRI of thorax to evaluate thymus (65% hyperplasia, 10% thymoma)

Treatment (*Neurology* 2021;96:114)

- Thymectomy if thymoma and in Ab ⊕ Pts w/o thymoma (*NEJM* 2016;375:511)
- Cholinesterase inhibitor (eg, pyridostigmine) is most rapid acting (30–60 min). Less effective for MusK MG. Side effects: cholinergic stim (brady, diarrhea, drooling).
- Immunosuppression: prednisone (benefit in wks; don't start during crisis) + steroid-sparing agent: AZA (benefit in 6–15 mo), MMF. Refractory: rituximab, MTX, eculizumab.
- Myasthenic crisis: treat precipitant; d/c cholinesterase inhibitor if suspect cholinergic crisis. IVIg or plasmapheresis; if no response, high-dose glucocorticoids (monitor for initial worsening). ICU if rapid or severe (preemptive intubation if FVC <20 mL/kg, NIF <30 cm H_2O).

Myopathies

Etiologies (*Neurol Clin* 2014;15:569)

- Hereditary: Duchenne, Becker, limb-girdle, myotonic, metabolic, mitochondrial
- Endocrine: hypothyroidism, hyperparathyroidism, Cushing syndrome
- Toxic: statins, fibrates, steroids, zidovudine, EtOH, cocaine, colchicine, penicillamine
- Infectious: HIV, HTLV-1, trichinosis, toxoplasmosis, COVID-19
- Inflammatory: poly-/dermatomyositis, inclusion body myositis, anti-HMGCR, ICI-related

Clinical manifestations

- Progressive or episodic weakness (not fatigue)
- Weakness most often symmetric, proximal > distal (stairs, rising from sitting, etc.)
- ± Myalgias (though not prominent or frequent), cramps, myotonia (impaired relaxation)
- May develop either pseudohypertrophy (dystrophies) or mild muscle atrophy
- Assoc. organ dysfxn: cardiac (arrhythmia, CHF), pulmonary (ILD), dysmorphic features

Diagnostic studies

- CK, aldolase, LDH, electrolytes, ALT/AST, PTH, TSH, ESR, HIV
- Autoantibodies: ANA, RF, anti-Jo1, antisynthetase, anti-Mi-2, anti-SRP, anti-HMGCR, 5TN1CA (in inclusion body myositis)
- EMG/NCS: low-amplitude, polyphasic units w/ early recruitment, ± fibrillation potentials
- Muscle biopsy, molecular genetic testing (where indicated)
- Age-appropriate cancer screening if polymyositis or dermatomyositis suspected

HEADACHE

Primary headache syndromes (*Cephalgia* 2018;38:1 & *Continuum* 2024;30:391)

- **Tension-type:** bilateral, pressure-like pain of mild–mod intensity, not throbbing or aggra-vated by

physical activity. A/w photophobia or phonophobia, not N/V. Freq a/w myofascial sensitivity in neck/head. Triggers: stress, sleep deprivation, dehydration, hunger. Episodic HA Rx: NSAIDs, acetaminophen (risk of med overuse HA); chronic HA Rx: TCAs.

- **Cluster HA** and other trigeminal autonomic cephalalgias (TACs) (*Continuum* 2018;24:1137)
  Characterized by unilateral headache a/w ipsilateral autonomic sx (rhinorrhea, red/tearing eye, miosis, ptosis, lid edema, sweating), subtypes differentiated by timing
  Cluster: ♂ > ♀, unilateral pain w/ autonomic sx & restlessness; attacks 15 min–3 h, up to 8/d (circadian). Rx: high-flow O_2 (12–15 L/min), sumatriptan. Ppx: CCB (verapamil).
  Paroxysmal hemicrania: similar to cluster, but ♀ > ♂, attacks 2–30 min. Rx: indomethacin.
  Hemicrania continua: ♀ > ♂, ice pick–like pain lasting >3 mo. Rx: indomethacin.
  Short-lasting unilateral neuralgiform HA (SUNA/SUNCT): ♂ > ♀, excruciating, stabbing, electrical pain, 5 sec–4 min, up to 200×/d. Rx: lamotrigine, gabapentin, IV lidocaine.
- **Migraine:** *vide infra*

Secondary causes of headaches (*Neurology* 2019;92:134)

- Traumatic: post-concussion, SAH, SDH, postcraniotomy-related pain
- ↑ ICP: mass (tumor, abscess, vascular malformations, ICH), hydrocephalus, idiopathic intracranial hypertension (pseudotumor cerebri), altitude-associated cerebral edema
- ↓ ICP: post-LP headache, CSF leak/dural tear, overshunting
- Vascular: stroke (esp. posterior circ), dissection, vasculitis (incl. GCA), reversible cerebral vasoconstriction syndrome (RCVS), ICH, venous sinus thrombosis (high pressure)
- Meningeal irritation: meningitis, SAH
- Extracranial: sinusitis, TMJ syndrome, glaucoma
- Systemic: hypoxia (OSA), hypercapnia, dialysis, HTN, cardiac cephalalgia, hypoglycemia, ↓ TSH, pheo, medication overuse (analgesics), withdrawal (caffeine, opioids, estrogen)

Clinical evaluation (*Neurology* 2019;92:134 & *JAMA* 2021;325:1874)

- Hx: onset (sudden vs. gradual), quality, evolution (progressive), severity, location, duration, triggers, alleviating factors, positional, hormonal (menstruation), preceding trauma, assoc. sx (visual Δs, "floaters," N/V, photophobia, focal neuro sx), meds (new, analgesics), substance abuse (opioids, caffeine), personal/family hx of HA; neoplasm, preg
- General and neurologic exam w/ fundoscopy. Headache diary.
- **Warning signs (should prompt neuroimaging)**
  Sudden onset, reaches max intensity w/in min, thunderclap; "worst HA of life" (SAH, RCVS, vascular); *meningismus* (SAH, infxn)
  Positional: lying > standing (↑ ICP); *N/V* (↑ ICP; migraines); coughing/bearing down (↑ ICP)
  Visual sx: diplopia, blurring, ↓ acuity (GCA, glaucoma, ↑ ICP); *eye pain* (glaucoma, trigeminal autonomic cephalalgia, optic neuritis)
  Abnl exam, papilledema; ↓ *consciousness*; systemic sx (fever)
  Age >65 y; immunosuppression (CNS infections), HTN/medication side effects (PRES)
  Hypercoagulability or OCP usage: consider venous imaging
- Imaging: CT or MRI; consider CTA (beading in vasculitis/RCVS/vasospasm), CTV/MRV
- LP if ? SAH (✓ for xanthochromia), idiopathic intracranial HTN (✓ opening press); image first!

Migraine (*NEJM* 2017;377:553)

Definition & clinical manifestations (*Lancet* 2018;391:1315 & *Continuum* 2021;27:586)

- **Epidemiology:** affects 15% of women and 6% of men; onset usually by 30 y
- **Migraine w/o aura** (most common): ≥5 attacks lasting 4–72 h with both (a) N/V *or* photophobia & phonophobia, and (b) ≥2 of following: unilateral, pulsating, mod–severe intensity, or aggravated by routine activity
- **Migraine w/ aura:** ≥2 attacks w/: (a) aura defined as ≥1 fully reversible sx: visual Δs (flickering

spots, visual loss), sensory sx (paresthesias, numbness), speech disturbance; *and* (b) unilateral progression of sx over ≥5 but ≤60 min; *and* (c) HA w/in 60 min of aura
- Aura may occur w/o HA ("acephalgic migraine"), must r/o TIA/stroke (typically rapid onset)
- If motor weakness, consider **sporadic or familial hemiplegic migraine**: aura of reversible motor weakness (up to 24 h), a/w CACNA1A, ATP1A2, or SCN1A mutations
- Precipitants: stress, foods (cheese, chocolate, MSG), fatigue, EtOH, menses, exercise

Treatment (*Lancet* 2021;397:1505 & *Continuum* 2024;30:344)

- Abortive: 5-HT_1 agonists (triptans) effective if given early; contra. if motor aura, CAD, stroke
- Also consider acetaminophen, NSAIDs, steroids, Mg, metoclopramide, prochlorperazine, valproate, dihydroergotamine (caution if CAD/triptan use), CGRP receptor antagonists (*Lancet* 2025;405:1014), neuromodulator devices. *Avoid butalbital, opioids.*
- Prophylaxis: AEDs (topiramate, VPA), βB (propranolol), TCAs (amitriptyline), Mg+B_2 daily suppl., botox/TPI, occipital nerve block, anti-CGRP, anti-PACAP (*NEJM* 2024;391:800)

BACK AND SPINAL CORD DISEASE

Differential diagnosis of back pain

- **Musculoskeletal:** involving spine (vertebrae, facet joints), paraspinal muscles & ligaments, sacroiliac joint, or hip joint. Spondylolisthesis, vertebral fx, OA, inflam. spondyloarthritis (qv), musculoligamentous "strain," myofascial pain syndrome, trochanteric bursitis.
- **Spinal cord** (myelopathy)**/nerve root** (radiculopathy):
  Degenerative/traumatic: disc herniation, foraminal or lumbar stenosis, spondylolisthesis
  Neoplastic: lung, breast, prostate, RCC, thyroid, colon mets, myeloma, lymphoma
  Infectious: osteomyelitis/discitis, epidural abscess, zoster, Lyme, CMV, HIV, spinal TB
  Vascular: spinal cord ischemia, dural AV fistula
- **Referred pain from visceral disease:**
  GI: PUD, cholelithiasis, pancreatitis, pancreatic cancer
  GU: pyelonephritis, nephrolithiasis, uterine or ovarian cancer, salpingitis
  Vascular: aortic dissection, leaking aortic aneurysm

Initial evaluation (*Lancet* 2017;389:736 & *Continuum* 2021;27:12)

- **History:** location, timing (acute/subacute/chronic), worse w/ Valsalva, radiation, trauma, wt loss, cancer, fever, immunocompromised, IVDU, neurologic sx, saddle anesthesia, Lhermitte phenomenon, bowel/bladder/sexual sx (retention, incontinence)
- **General physical exam:** local tenderness, ROM, signs of infection or malignancy; paraspinal tenderness or spasm in musculoskeletal strain
- **Signs of radiculopathy** (sharp/lancinating pain radiating into limb):
  Spurling sign (cervical radiculopathy): radicular pain w/ downward force to extended & ipsilaterally rotated head; 30% Se, 93% Sp
  Straight leg raise (sciatica=lumbosacral radiculopathy): radicular pain at 30–70°; ipsilateral: 92% Se, 28% Sp; crossed (contralateral leg raised): 28% Se, 90% Sp
  Patrick/FABER test (SI joint synd): severe pain on hip ext rotation; 70% Se, 100% Sp
  Neurogenic claudication in lumbar stenosis (see table on next page)
- **Neuro exam:** full motor (incl. sphincter tone); gait; sensory (temp/pain, position, vibration; ± perineal; ? dermatomal); reflexes incl. bulbocavernosus, anal wink (S4), cremasteric (L2)
- **Red flags:** acute change (pain, weakness), upper motor neuron signs (hyperreflexia, upgoing toes), cauda equina or conus medullaris syndromes (saddle anesthesia, bowel/bladder or sexual dysfunction, reduced rectal tone, loss of sacral reflexes), dyspnea when flat (C3–C5), pain at rest

or at night
- **Laboratory** (depending on suspicion): CBC w/ diff, ESR/CRP, Ca, PO_4, CSF, BCx
- **Neuroimaging:** low yield if nonradiating pain, high false ⊕ rate (incidental spondylosis); X-rays, CT (low sensitivity for spine/roots), CT myelography, MRI, bone scan
- **EMG/NCS:** may be useful to distinguish root/plexopathies from peripheral neuropathies

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Spinal Cord Compression

Clinical features (*Continuum* 2021;27:163)

- Etiologies: **tumor** (vertebral mets, intradural meningioma/neurofibroma), **epidural abscess/ hematoma**, vascular malformation (dural AV fistula), degen. dis. (spondylosis), trauma
- Acute: flaccid paraparesis and absent reflexes ("spinal shock")
- Subacute–chronic: spastic paraparesis and hyperreflexia (upgoing toes ± ankle clonus)
- Posterior column dysfunction in legs (loss of vibratory and/or proprioceptive sense)
- Sensory loss below level of lesion (truncal sensory level ± bilateral leg sx localize to cord)

Evaluation & treatment

- Empiric spine immobilization (collar, board) for all trauma patients
- STAT MRI (at and above clinical spinal level, with gadolinium) or CT myelogram
- Emergent neurosurgical and/or neurology consultation. Urgent radiation therapy ± surgery if compression due to metastatic disease (*Lancet Oncol* 2017;18:e720).
- Empiric broad-spectrum antibiotics ± surgery if c/f epidural abscess
- High-dose steroids depending on cause:
  - Tumor: dexamethasone 16 mg/d IV (8 mg twice a day) with slow taper over weeks
  - Trauma: methylprednisolone 30 mg/kg IV over 15 min then 5.4 mg/kg/h × 24 h (if started w/in 3 h of injury) or × 48 h (if started 3–8 h after injury) (*Cochrane* 2012;CD001046)

Nerve Root Compression

Clinical features (*NEJM* 2015;372:1240 & *Continuum* 2021;27:163)

- Radicular pain aggravated by activity (esp. bending, straining, coughing), relieved by lying
- Sciatica = radicular pain radiating from buttocks down lateral aspect of leg, often to knee or lateral calf ± numbness and paresthesias radiating to lateral foot. Caused by compression of nerve roots, plexus, or sciatic nerve.

Pathophysiology

- <65 y: 90% from disc herniation. ≥65 y also w/ more degenerative contributors: ligamentous hypertrophy, osteophyte formation, facet arthropathy, neural foraminal narrowing.
- Spinal stenosis: central canal narrowing → root compression via direct impingement, CSF flow obstruction, vascular compromise

Disc Herniation: Cervical and Lumbar Radiculopathy					
Disc	**Root**	**Pain/Paresthesias**	**Sensory Loss**	**Motor Loss**	**Reflex Loss**
C4–C5	C5	Neck, shoulder, upper arm	Shoulder, lateral arm	Deltoid, biceps, infraspinatus	Biceps
C5–C6	C6	Neck, shoulder, lat. arm, radial forearm, thumb, & index finger	Radial forearm, thumb, & index finger	Biceps brachioradialis	Biceps, brachioradialis
C6–C7	C7	Neck, lat. arm, ring & index fingers	Index & middle fingers	Triceps, extensor carpi ulnaris	Triceps
C7–T1	C8	Ulnar forearm and hand	Ulnar half of ring finger, little finger	Intrinsic hand muscles, flexor dig profundus	Finger flexion
L3–L4	L4	Anterior thigh, inner shin	Anteromedial lower leg, inner foot	Quadriceps	Patellar
L4–L5	L5	Lat. thigh & calf, dorsum of foot, great toe	Lat. calf & great toe	Foot dorsiflex., invers. & evers., toe extension	Medial hamstring
L5–S1	S1	Back of thigh, lateral posterior calf, lat. foot	Lateral foot & toes, sole of foot	Gastrocnemius	Achilles

Nb, lumbar disc protrusion tends to compress the nerve root that exits 1 vertebral level below the protrusion

Neurogenic vs. Vascular Claudication		
Features	**Neurogenic Claudication**	**Vascular Claudication**
Cause	Lumbar spinal stenosis (with nerve root compression)	Peripheral artery disease (with limb ischemia)
Pain	Radicular back/buttock pain Radiating down legs	Cramping leg pain Mostly in calves; radiating up legs
Worse with	Walking & standing Hyperextension/lying prone	Walking Biking
Better with	Bending forward, sitting	Rest (standing or sitting)
Other sx	Numbness/paresthesias	Pale, cool extremity
Exam	± Focal weakness, ↓ reflexes ↓ Lumbar extension Preserved pulses	Diminished/absent pulses (dorsalis pedis/posterior tibialis) Pallor
Diagnostic studies	MRI lumbar spine CT myelogram (if no MRI) EMG/NCS	Arterial Doppler studies Ankle-brachial index (ABI) Arteriography

Treatment	PT (flexion exercise), NSAIDs, epidural steroid injections (ESI) Surgery (if other Rx fails)	Modify vascular risk factors, exercise rehab, antiplatelet Rx, revascularization

Nb, diagnosis complicated by overlap & possibility of both diagnoses in the same patient

Evaluation & treatment of nerve root compression (*NEJM* 2016;374:1763)

- MRI if sx not improved after 6 wk of conservative tx; if nondiagnostic, consider EMG/NCS
- Conservative: avoid bending/lifting; soft collar (cervical radiculopathy); NSAIDs; muscle relaxants; lidocaine patch/ointment; Rx neuropathic pain (see “Peripheral Neuropathies”); physical/occup therapy. Insufficient evidence for oral steroids.
- Avoid opioids when possible; risks outweigh benefits in noncancerous back pain
- Spinal epidural steroid injections (ESI): limited short-term relief of refractory radicular pain
- Surgery: indicated in cord compression or cauda equina syndrome; progressive motor dysfunction or EMG/NCS pathologic findings; bowel/bladder dysfunction; intractable pain w/ failure to respond to conservative Rx after 3 mo

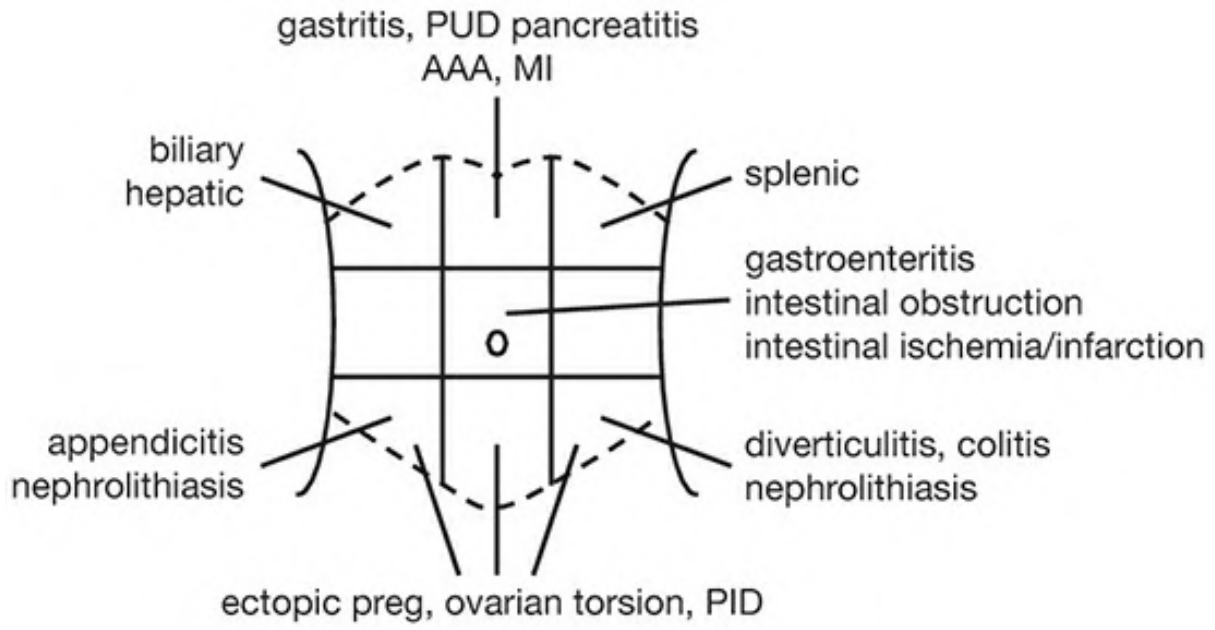
SURGICAL ISSUES

Abdominal Pain

Visceral Pain		
Anatomic Division	**Viscera**	**Area to Which Pain Referred**
Foregut	Esophagus & duodenum	Epigastrium
Midgut	Jejunum to mid-transverse colon	Umbilicus
Hindgut	Mid-transverse colon to rectum	Hypogastrium

Pain due to pancreatitis and nephrolithiasis commonly radiates to the back

Figure 10-1 Etiologies of abdominal pain based on location



Initial evaluation

- History: onset of pain, location, exacerbating/relieving factors
- Assoc. sx: fevers/chills, N/V, Δ in bowel habits (diarrhea/constipation, stool diam. or color, hematochezia, melena), flatus, jaundice, Δ in urine color, Δ in wt, menstrual hx in women
- PMHx: previous incisions or abdominal surgeries; Ob/Gyn hx
- Exam: VS; general posture of Pt; comprehensive abdominal exam looking for signs of peritonitis, which include rebound tenderness and involuntary guarding, abdominal wall rigidity, pain w/ percussion/minimal palpation; presence of hernias; rectal/pelvic
- Labs: CBC, electrolytes, LFTs, amylase/lipase, pregnancy test
- Imaging: depends on suspected etiology, may include RUQ U/S for biliary/hepatic disease, KUB for intestinal obstruction, CT for pancreatitis or intestinal disease. Do not delay resuscitation or surgical consultation for ill Pt while waiting for imaging.

Acute Abdomen

Definition

- Acute-onset abdominal pain that portends need for urgent surgery

Etiologies

- Perforated viscus → peritonitis (perforated ulcer, complicated diverticulitis, trauma)
- Intraperitoneal or retroperitoneal bleed (also see “Acute Aortic Syndromes”)
- Bowel obstruction (adhesions from previous surgeries, malignancies, hernias, volvulus)
- Acute mesenteric ischemia (esp. if AF, low-flow states, “pain out of proportion to exam”)
- Mimics: severe pancreatitis can resemble peritonitis; renal colic causes severe abdominal pain but not abdominal rigidity

Initial evaluation

- H&P as above
- Labs as above plus: PT/INR, PTT, lactate, type & screen (crossmatch if active bleeding)
- Imaging: upright CXR/KUB; if stable, CT A/P w/ IV contrast (IV/PO if suspect obstruction)

Initial management

- Immediate surgical consultation for suspected acute abdomen
- NPO, start IV fluids (NS or LR), Foley, NGT placement if obstruction suspected
- Broad spectrum abx if perforation suspected

Extremity Emergencies

Acute limb ischemia (see “Peripheral Artery Disease” for details)

- Definition: sudden ↓ in perfusion causing threat to limb viability
- Eval: detailed vascular exam (incl. pulses & Doppler signals, motor/sensory function); CTA
- Initial management: anticoag for embolism/thrombosis (heparin dose 80 U/kg bolus, then 18 U/kg drip); immediate surgical consultation

Compartment syndrome (*Clin Orthop Relat Res* 2010;468:940)

- Definition: ↑ intracompartmental pressure w/ compressive closure of venules → ↑ hydrostatic force resulting in further increases in compartment pressure
- Etiologies: orthopedic (fracture), vascular (ischemia–reperfusion), iatrogenic (eg, vascular injury in anticoagulated Pt), soft-tissue injury (eg, prolonged limb compression)
- Clinical manifestations: pain espec. on passive movement, swollen/tense compartment, paresthesia, pallor, pulselessness, paralysis (late)
- Evaluation: surgical evaluation of compartment pressures; intracompartment pressure >30 or difference between diastolic & intracompartment pressure of >10–30 is diagnostic
- Treatment: fasciotomy

Surgical Tubes, Drains, Wounds

Tracheostomy (*Otolaryngol Head Neck Surg* 2013;148:6)

- Typically a cuffed tube, which creates a tight seal to facilitate ventilation throughout tube
- Speaking valve (eg, Passy-Muir): 1-way valve that allows inhalation through tube, but exhalation

around tube through vocal cords (nb, cuff should not be inflated)
- 1st routine tube Δ for *percutaneously* placed tubes should be ~10 d post-op; *surgically* placed tubes can be Δ'd >5 d post-op; first Δ should be overseen by experienced person
- Accidental dislodgment: intubate from above (if airway/vent nec & anatomically possible)
  w/in 7 d of placement: emergent surgical consultation
  >7 d after placement: replace with a similar size tube or smaller

Chest tubes (*Eur J Cardiothorac Surg* 2011;40:291; *JAMA Surgery* 2022;15:3)

- Inserted for PTX, chest trauma, or after thoracic surg for drainage of air/fluid. Range from small (8–14 Fr for spont. PTX, effusions) to large (24–32 Fr for resection). Smaller tubes can be placed percutaneously by surgical team or interventional pulmonology.
- Connected to 3-chamber chest drainage system:
  1st: collection chamber for pleural fluid
  2nd: water seal chamber used to allow air to exit pleural space on exhalation and prevent air from entering on inhalation
  3rd: suction control chamber which regulates suction transmitted to pleural space
- Monitor for output and presence of air leak (indicated by bubbling in *water seal chamber*)
- Removal determined by overall daily outputs and absence of air leak
- If accidentally removed or dislodged, tube should be completely removed and an occlusive dressing (eg, 4 × 4 covered w/ Tegaderm or silk tape) should be placed *rapidly* over site. CXR STAT; new tube should be placed if persistent PTX.

Gastrostomy/jejunostomy tubes (*Paediatr Child Health* 2011;16:281)

- Placed for tube feedings, hydration, and delivery of medications
- Should not be removed for ≥6–8 wk to allow establishment of mature tract
- Obstructed tubes can be cleared by flushing with agents such as carbonated water, meat tenderizer, & pancreatic enzymes. ↓ obstruction by flushing before & after meds and flushing q4–6h when receiving continuous feeds.
- Inadvertent removal: place Foley catheter of similar size or smaller into tract *immediately* to prevent stoma from closing. Tube then replaced and confirmed via fluoro study.

Suture/staple removal

- Should be done in consultation w/ surgical team; timing depends on location of wound
- *Should not be removed if there is evidence of wound separation during removal!*
- After removal, wound should be reapproximated w/ Steri-Strips

Decubitus ulcers (*J Wound Ostomy Continence Nurs* 2012;39:3)

- Sores in dependent areas exposed to repeated pressure (commonly sacrum, heels)
- Risk factors: immobility, poor nutritional status
- Stage I (non-blanchable erythema); Stage II (partial thickness); Stage III (full-thickness skin loss); Stage IV (full-thickness tissue loss)
- Treatment: offload area, air mattress, pillows and/or support boots, nutritional support
- Surgical consultation for debridement of ulcers with necrotic or infected tissue, may require plastic surgical reconstruction for advanced ulcers once clean

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Maximizing a Surgical Consult

- For ill Pt, call surgical consult early, do not wait for labs & imaging results
- If potential surgical emergency, make Pt NPO, start IVF, ✓ coags, type & screen
- Have appropriate-level MD who knows & has examined Pt call consult

OB/GYN ISSUES

Vaginal Bleeding

Bleeding from lower (vulva, vagina, cervix) or upper genital tract (uterus)

Etiologies

- Premenopausal
  - Not pregnant: menses, lower tract (trauma, STI, cervical dysplasia/cancer), & abnormal uterine bleeding (polyp, adenomyosis, leiomyoma, hyperplasia/cancer, coagulopathy, ovulatory dysfunction, endometrial, & iatrogenic)
  - Pregnant
    - 1st trimester: threatened abortion, spont. abortion (missed, incomplete, or complete), ectopic preg, molar preg (partial/complete hydatidiform mole)
    - 2nd or 3rd trimester: preterm labor/labor, placenta previa, placental abruption
- Postmenopausal: atrophy, polyp, leiomyoma, endometrial hyperplasia/cancer

History & exam

- Age, menopausal status, gestational age if preg, volume & duration of current bleeding
- If premenopausal: menstrual hx including age of onset, interval between & duration of menses, any assoc. sx & LMP to assess timing of menstrual cycle
- Past Ob/Gyn hx: incl. any structural abnl, STI, & contraception
- Health maint.: Pap smear, HPV screening, domestic violence, anticoag/antiplt meds
- General physical & abdominal exam (incl. tenderness, masses)

- Pelvic exam: external (quantity of bleeding seen on vulva, any lesions, any trauma), speculum exam (quantity of bleeding, cervical os open/close; & if open, dilation, any polyps), & bimanual exam (cervical dilation, uterine size/tenderness, adnexal mass/tenderness)

Laboratory evaluation & imaging

- Urine (rapid test) & serum preg test **(**βhCG), Hct/hemoglobin

- Pelvic U/S: visualize leiomyoma & if preg, intrauterine preg & placental position to r/o placenta previa/abruption
- If preg & intrauterine preg not seen, *must r/o ectopic as life-threatening dx* (βHCG > discrim. zone → ? ectopic; if βHCG <discrim. zone → follow βHCG) (*JAMA* 2013;309:1722)

Vaginal Discharge

Fluid or mucus from vagina, cervix, or uterus

Etiologies

- Infectious: bacterial vaginosis, candida vulvovaginitis, trichomoniasis
- Noninfectious: physiologic (in preg/non-preg), rupture of membranes, foreign-body rxn

Initial evaluation

- Age, LMP, gestational age if preg or menopausal status
- Discharge quantity, color, consistency, odor, assoc. sx (itchiness, redness, abd/pelvic pain)

- Past Gyn hx: incl. STI and contraception usage (condoms ↓ STI risk)
- Tampon or condom use as risk factors for retained foreign body
- Pelvic exam: external (quantity & quality of discharge on vulva, any lesions), speculum (discharge, appearance of cervix), bimanual (cervical motion tenderness)
- Laboratory: pH of discharge, microscopy (saline & KOH wet mounts), urine preg test

Treatment

- Bacterial vaginosis: oral/vaginal metronidazole or clindamycin
- Candida vulvovaginitis: oral/topical antimycotic medications
- Trichomoniasis: oral metronidazole

Adnexal Mass in Non-Pregnant Woman

Mass arising from ovary, fallopian tube, or surrounding connective tissue

Etiologies

- Ovarian: functional cyst (follicular/corpus luteum), hemorrhagic cyst, endometriomas, ovarian torsion, tubo-ovarian abscess, benign & malignant ovarian tumors
- Fallopian tube: paratubal cyst, hydrosalpinx, ovarian torsion, tubo-ovarian abscess

Initial evaluation

- LMP/menopausal status, assoc. sx of abd/pelvic pain, FHx of gyn cancers
- Abd exam (distension, tenderness, masses), bimanual (uterine or adnexal masses)
- Preg test if premenopausal (if ⊕, then mass likely preg), CA-125 if postmenopausal
- Pelvic U/S (even if mass 1st identified on CT, because U/S is best modality), U/S appearance of mass important factor to determine risk of malignancy

OPHTHALMIC ISSUES

Initial Evaluation

- Ocular sx: onset (sudden or progressive) & duration of sx; unilateral vs. bilateral; pain; photophobia; discharge; Δ in near (eg, book) or far (eg, TV across room) vision
- Preexisting ocular conditions, eye meds (incl any Δs), recent h/o ocular surgery, trauma
- Ocular exam: vision (✓ with Pt's correction [glasses/contacts]) w/ each eye; pupillary exam; EOM; confrontation visual fields (important if suspect CNS problem)
- Overall: VS, immunocomp., s/s of infxn, h/o malig, CNS issues, Δ in meds, CBC, coags

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Common Visual Symptoms

- **Fluctuation in vision (ie, blurry):** med-induced refractive error (eg, systemic steroids, chemo), hyperglycemia, dry eye (common). **Visual defect** may p/w "blurred vision." Bilateral: glaucoma (common), homonymous contral. CNS lesion; bitemporal: pituitary, toxic/nutritional. Unilateral: ipsilateral orbital, retinal, or optic nerve lesion.
- **Red eye:**
  - Bilateral: viral conjunct. (starts in 1 eye; also w/ lid swelling, discharge); chronic inflammation (dry eyes, rosacea, autoimmune disease), Chlamydial infection
  - Unilateral: subconj. hem., infxn (HSV), or inflam (eg, episcleritis, iritis, uveitis, scleritis); acute angle closure (qv). Scleritis & acute angle closure p/w severe pain, H/A, nausea.
- **Double vision (diplopia):** fixed double vision w/ ophthalmoplegia from orbital process or cranial nerve palsy (III, IV, VI). Transient "diplopia" due to fatigue or sedation.

- **Flashing lights/floaters:** vitreous detach. (common, benign); retinal detach. (unilateral visual field defect; urgent ophthalmology consult); hemorrhage; intraocular lymphoma

Acute Visual Changes

Etiologies of Acute Vision Loss (italics indicates a/w pain)		
	Unilateral	**Bilateral**
Transient (<24 h, often <1 h)	Ret. art. embolism, impending retinal artery (amaurosis fugax) or vein occlusion, vasospasm, carotid dis.	Ocular surface dis. (dry eye), bilat. carotid dis., TIA, migraine, high ICP (papilledema)
Prolonged (>24 h)	Retinal art/vein occl, retinal detach., retina/vitreous heme, retinitis, ant. optic neurop./*corneal ulcer, GCA, acute angle closure glaucoma*	Visual cortex stroke, post. ischemic neuropathy (profound hypotension during surgery), post. reversible enceph. synd., *GCA*

Common Ocular Conditions (front to back)

- **Orbit:** **orbital cellulitis** (fever, proptosis, ↓ EOM; *emergent abx, scan, & referral*)
- **Lids:** hordeolum or chalazion (stye); preseptal cellulitis; **ptosis** (age; Horner's; **CN III palsy:** EOM restricted in all directions except laterally (eye is "down & out"), a/w ptosis & mydriasis, seen w/ uncal herniation, aneurysm of post com art., GCA, HTN, DM); incomplete lid closure (**CN 7th palsy**)
- **Conjunctiva:** conjunctivitis (**red eye,** viral or bacterial); subconj. hemorrhage (HTN, blood thinner); ocular surface disease (dry eyes); episcleritis/scleritis (deep vessels of sclera)
- **Cornea:** **contact lens–related ulcer;** herpetic keratitis/scarring/neurotropic ulcers **(CN V paresis);** pterygium; keratoconus; corneal dystrophy, med toxicity (amio, ADCs)
- **Ant. chamber:** iritis (inflam. cells); hyphema (blood, post trauma); hypopyon (inflam./infxn)
- **Pupil:** Anisocoria (physiologic asymmetry); Horner's, CN III
- **Lens:** cataract (age, trauma, medication, radiation, congenital); post cataract surgery infxn
- **Vitreous/Retina/Macula:** diabetic retinopathy; macular degen; retinal detachment; retinal ± vitreous hemorrhage; retinitis (infectious), medication toxicity
- **Optic nerve (CN II):** ischemic neuropathy p/w acute unilat. visual loss, altitudinal field defect; a/w GCA; nonarteritic a/w HTN, hyperchol., DM, thrombophilia. Optic neuritis: often p/w unilat. central scotoma, pain w/ EOM, ↑ visual loss over days; a/w demyelinating disease (eg, MS), also seen w/ sarcoidosis & CTD. Optic neuropathy (glaucoma common).

Ocular Emergencies

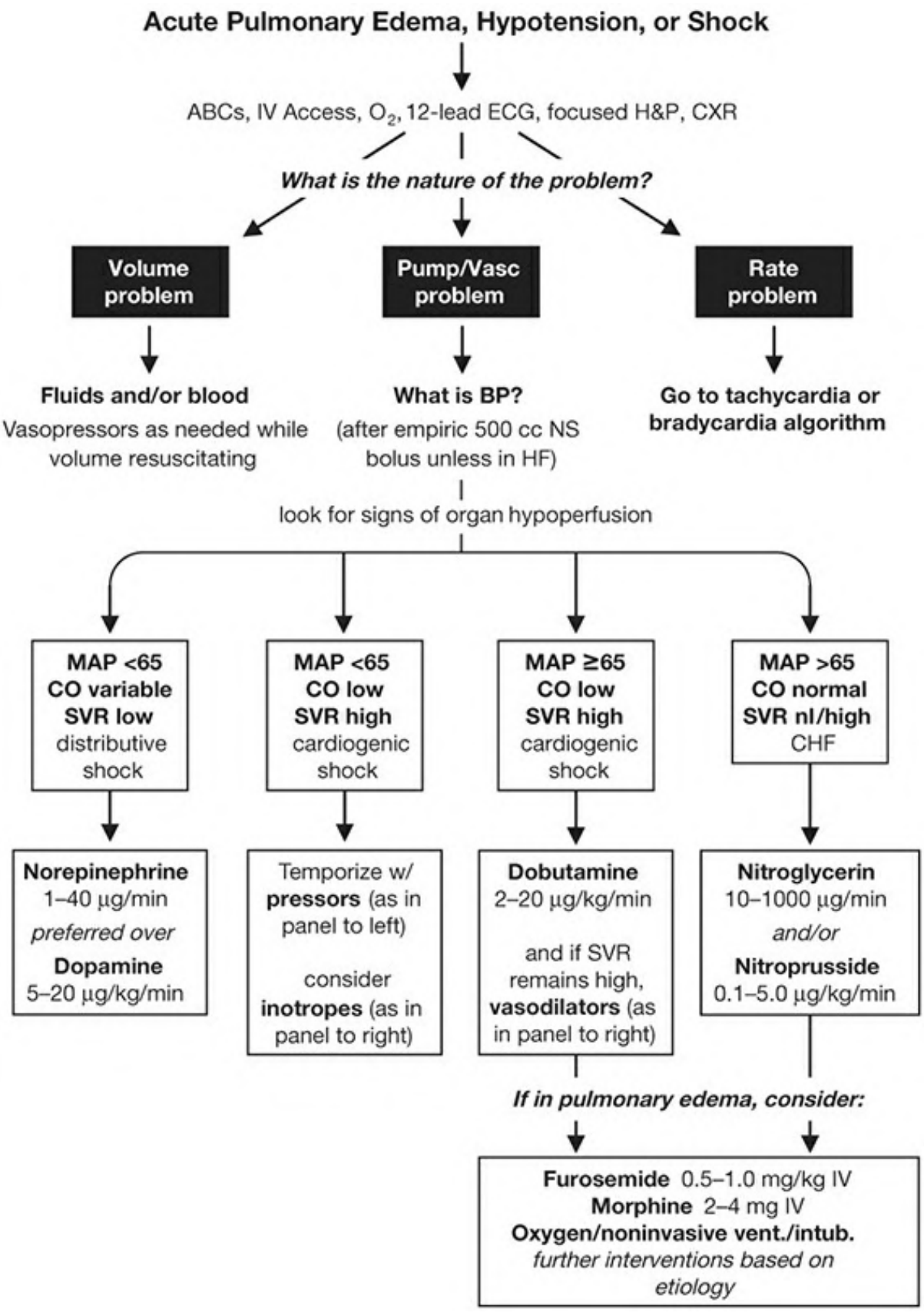
- **Chemical splash:** alkali worse than acid; immediate eye flush; pH 7.3–7.4 normal
- **Acute angle closure glaucoma:** fixed mid-dilated pupil, corneal edema, high intraocular pressure (typically >50; normal 8–21). Rx w/ topical drops; may require AC tap/laser.
- **Penetrating eye injury:** protect eye (no patching), IV abx, tetanus, NPO, surgical prep

ICU MEDICATIONS

Drug	Class	Dose	
		per kg	average
Pressors, Inotropes, and Chronotropes			
Phenylephrine	α_1	10–300 μg/min	
Norepinephrine	$\alpha_1 > \beta_1$	1–40 μg/min	
Vasopressin	V_1	0.01–0.1 U/min (usually <0.04)	
Epinephrine	$\alpha_1, \alpha_2, \beta_1, \beta_2$	2–20 μg/min	
Isoproterenol	β_1, β_2	0.1–10 μg/min	
Dopamine	D β, D α, β, D	0.5–2 μg/kg/min 2–10 μg/kg/min >10 μg/kg/min	50–200 μg/min 200–500 μg/min 500–1000 μg/min
Dobutamine	$\beta_1 > \beta_2$	2–20 μg/kg/min	50–1000 μg/min
Milrinone	PDE	±50 μg/kg over 10 min then 0.25–0.75 μg/kg/min	3–4 mg over 10 min then 20–50 μg/min
Vasodilators			
Nitroglycerin	NO	5–500 μg/min	
Nitroprusside	NO	0.25–10 μg/kg/min	10–800 μg/min
Labetalol	α_1, β_1, and β_2 blocker	20–80 mg q10min or 10–120 mg/h	
Fenoldopam	D	0.1–1.6 μg/kg/min	10–120 μg/min
Clevidipine	CCB	1–32 mg/h	
Epoprostenol	vasodilator	2–20 ng/kg/min	
Antiarrhythmics			
Amiodarone	K et al. (Class III)	150 mg over 10 min, then 1 mg/min × 6 h, then 0.5 mg/min × 18 h	
Lidocaine	Na channel (Class IB)	1–1.5 mg/kg then 1–4 mg/min	100 mg then 1–4 mg/min
Procainamide	Na channel (Class IA)	17 mg/kg over 60 min then 1–4 mg/min	1 g over 60 min then 1–4 mg/min
Ibutilide	K channel (Class III)	1 mg over 10 min, may repeat × 1	
Propranolol	β blocker	0.5–1 mg q5min then 1–10 mg/h	
Esmolol	$\beta_1 > \beta_2$ blocker	500–1000 μg/kg then 50–200 μg/kg/min	20–40 mg over 1 min then 2–20 mg/min
Verapamil	CCB	2.5–5 mg over 1–2′, repeat 5–10 mg in 15–30′ prn 5–20 mg/h	
Diltiazem	CCB	0.25 mg/kg over 2 min reload 0.35 mg/kg × 1 prn then 5–15 mg/h	20 mg over 2 min reload 25 mg × 1 prn then 5–15 mg/h
Adenosine	purinergic	6 mg rapid push; if no response: 12 mg → 12–18 mg	
Sedation			
Morphine	opioid	1–30 (in theory, unlimited) mg/h	
Fentanyl	opioid	50–100 μg then 50–800 (? unlimited) μg/h	
Propofol	anesthetic	1–3 mg/kg then 0.3–5 mg/kg/h	50–200 mg then 20–400 mg/h
Dexmedetomidine	α_2 agonist	1 μg/kg over 10 min → 0.2–0.7 μg/kg/h	
Diazepam	BDZ	1–5 mg q1–2h then q6h prn	
Midazolam	BDZ	0.5–2 mg q5min prn; 0.02–0.1 mg/kg/h or 1–10 mg/h	
Lorazepam	BDZ	0.01–0.1 mg/kg/h	
Naloxone	opioid antag.	0.4–2 mg q2–3min to total of 10 mg	
Flumazenil	BDZ antag.	0.2 mg over 30 sec then 0.3 mg over 30 sec prn may repeat 0.5 mg over 30 sec to total of 3 mg	

Miscellaneous			
Aminophylline	PDE	5.5 mg/kg over 20 min then 0.5–1 mg/kg/h	250–500 mg then 10–80 mg/h
Octreotide	somatostatin analog	50 µg then 50 µg/h	
Glucagon	hormone	3–10 mg IV slowly over 3–5 min then 3–5 mg/h	
Mannitol	osmole	1.5–2 g/kg over 30–60 min repeat q6–12h to keep osm 310–320	

Figure 11-1 ACLS pulmonary edema, hypotension, or shock algorithm


Acute Pulmonary Edema, Hypotension, or Shock
ABCs, IV Access, O_2, 12-lead ECG, focused H&P, CXR
What is the nature of the problem?
Volume problem
Pump/Vasc problem
Rate problem
Fluids and/or blood
Vasopressors as needed while volume resuscitating
What is BP?
(after empiric 500 cc NS bolus unless in HF)
Go to tachycardia or bradycardia algorithm
look for signs of organ hypoperfusion
MAP <65
CO variable
SVR low
distributive shock
MAP <65
CO low
SVR high
cardiogenic shock
MAP ≥65
CO low
SVR high
cardiogenic shock
MAP >65
CO normal
SVR nl/high
CHF
Norepinephrine
1–40 μg/min
preferred over
Dopamine
5–20 μg/kg/min
Temporize w/ pressors (as in panel to left)
consider inotropes (as in panel to right)
Dobutamine
2–20 μg/kg/min
and if SVR remains high, vasodilators (as in panel to right)
Nitroglycerin
10–1000 μg/min
and/or
Nitroprusside
0.1–5.0 μg/kg/min
If in pulmonary edema, consider:
Furosemide 0.5–1.0 mg/kg IV
Morphine 2–4 mg IV
Oxygen/noninvasive vent./intub.
further interventions based on etiology

(Adapted from ACLS 2005 Guidelines)

ANTIMICROBIALS

The following tables of spectra of activity for different antimicrobials are generalizations. Sensitivity data at your own institution should be used to guide therapy.

Penicillins		
Generation	**Properties**	**Spectrum**
Natural (penicillin)	Active vs. many GPC, GPR, anaerobes (not *Bacteroides*), some Gram ⊖ coccobacilli & Gram ⊖ diplococci	Most streptococci, many enterococci, *Listeria, C. acnes, Pasteurella, Actinomyces*, syphilis
Anti-staph (eg, nafcillin)	Active vs. PCNase-producing Staph Little activity vs. Gram ⊖	Staphylococci (except MRSA) Streptococci
Amino (eg, ampicillin)	Penetrate porin channel of Gram ⊖ Not stable against PCNases	PCN plus *E. coli, Proteus, H. influenzae, Shigella*
Extended (eg, piperacillin)	Penetrate porin channel of Gram ⊖ More resistant to PCNases	Most GNR incl. *Enterobacter, Pseudomonas, Serratia*
β-lact. inhib. (eg, sulbactam, clavulanate) with PCN derivative	Inhibits some plasma-mediated β-lactamases	Adds staph (not MRSA), most PCN-R anaerobes, & some GNR (*H. flu, M. cat*, some enterics); intrinsic activity against *Acinetobacter baumannii*

Cephalosporins		
Resistant to most penicillin β-lactamases. No activity vs. enterococci.		
Generation	**Spectrum**	**Indications**
1st (eg, cefazolin)	Most GPC (incl. staph & strep, not MRSA); some GNR (incl. *E. coli*, *Proteus, Klebsiella*)	Used for surgical Ppx & skin infxns
2nd (eg, cefuroxime, cefotetan)	↓ activity vs. GPC, ↑ vs. GNR + some anaerobes 2 subgroups: Resp: *H. influenzae* & *M. catarrhalis* GI/GU: ↑ activity vs. *B. fragilis*	PNA/COPD flare Abdominal infxns
3rd (eg, ceftriaxone, ceftazidime)	Broad activity vs. GNR (not ESBL), streptococci, & some anaerobes. Ceftazidime active vs. *Pseudomonas*, less vs. strep.	PNA, sepsis, meningitis
4th (eg, cefepime)	↑ resistance to β-lactamases (incl. *Enterobacter*)	Similar to 3rd gen. Febrile neutropenia. Cefepime > ceftriaxone for MSSA (neither 1st line).
5th (eg, ceftaroline, ceftobiprole)	Only class of cephalosporin with MRSA activity. GN activity similar to ceftriaxone.	CAP, SSTI, MRSA. Ceftobiprole approved for MRSA bacteremia

	NOT active vs. *Pseudomonas*.	and R-NVE.
Combination (eg, ceftolozane-tazobactam, ceftazidime-avibactam)	MDR GNRs, incl. *Pseudomonas*. Ceftaz-avi has activity vs. some carbapenemases.	Complicated UTIs, complicated intra-abdominal infections, HAP/VAP

Other Beta-Lactams		
Class	**Properties**	**Spectrum**
Carbapenems (eg, imipenem)	Resistant to most β-lactamases	Most Gram ⊕ & ⊖, incl. anaerobes; *not* MRSA or VRE
Monobactams (aztreonam)	Active vs. Gram ⊖ but not Gram ⊕	Gram ⊖ bacterial infxn in Pt w/ PCN or Ceph allergy

Other Antimicrobials	
Antibiotic	**Spectrum**
Vancomycin	Gram ⊕ bacteria incl. MRSA, PCNase-producing pneumococci and enterococci (except VRE)
Linezolid	GPC incl. MRSA & VRE (check susceptibility for VRE)
Daptomycin	
Quinolones	GNR & atypicals. Levo and esp moxi ↑ activity vs. Strep/Staph spp.
Aminoglycosides	GNR. Synergy w/ cell-wall active abx (β-lactam, vanco) vs. GPC. ↓ activity in low pH (eg, abscess). No activity vs. anaerobes.
Macrolides	GPC, some respiratory Gram ⊖, atypicals
TMP/SMX	Most enteric GNR, Staph incl CA-MRSA, *Stenotrophomonas*, *Nocardia, Toxo*, *Pneumocystis*
Clindamycin	Most Gram ⊕ (except enterococci) & anaerobes (increasing resistance, especially GI)
Metronidazole	Almost all anaerobic Gram ⊖, most anaerobic Gram ⊕, some protozoa (*Entamoeba*, *Trichomonas*, etc.)
Doxycycline	*Rickettsia, Ehrlichia, Anaplasma, Chlamydia, Mycoplasma, Nocardia*, leptospirosis, Lyme; many Staph and GNR
Tigecycline	Many GPC incl. MRSA & VRE; most GNR incl. ESBL but not *Pseudomonas* or *Proteus*; most anaerobes
Durlobactam-sulbactam	Carbapenem-resistant *Acinetobacter baumannii*

Treatment for Common Fungi ("x" indicates activity, shaded boxes indicate 1st-line treatment)						
Antifungal	*C. albicans*	*C. glabrata & krusei*	*Crypto*	**Endemic** *Histo, Blasto, Coccidio*	*Aspergillus*	*Mucor*
Fluconazole	x		x			
Itraconazole	x		x	x		
Voriconazole	x	x	x	x	x	
Posaconazole	x	x	x	x	x	x
Isavuconazole	x		x	(x)	x	x
Micafungin	x	x			x	
Ampho B	x	x	x	x	x	x

FORMULAE AND QUICK REFERENCE

CARDIOLOGY

Hemodynamic Parameters	Normal Value
Mean arterial pressure $(MAP) = \frac{SBP + (DBP \times 2)}{3}$	70–100 mmHg
Heart rate (HR)	60–100 bpm
Right atrial pressure (RA)	≤6 mmHg
Right ventricular (RV)	systolic 15–30 mmHg diastolic 1–8 mmHg
Pulmonary artery (PA)	systolic 15–30 mmHg mean 9–18 mmHg diastolic 6–12 mmHg
Pulmonary capillary wedge pressure (PCWP)	≤12 mmHg
Cardiac output (CO)	4–8 L/min
Cardiac index $(CI) = \frac{CO}{BSA}$	2.6–4.2 L/min/m^2
Stroke volume $(SV) = \frac{CO}{HR}$	60–120 mL/contraction
Stroke volume index $(SVI) = \frac{CI}{HR}$	40–50 mL/contraction/m^2
Systemic vascular resistance (SVR) $= \frac{MAP - \text{mean RA}}{CO} \times 80$	800–1200 dynes × sec/cm^5

Pulmonary vascular resistance (PVR) $= \frac{\text{mean PA} - \text{mean PCWP}}{\text{CO}} \times 80$	120–250 dynes × sec/cm^5

"Rule of 6's" for PAC: RA ≤6, RV ≤30/6, PA ≤30/12, WP ≤12. Nb 1 mmHg = 1.36 cm water or blood.

Fick cardiac output

Oxygen consumption (L/min) = CO (L/min) × arteriovenous (AV) oxygen difference
CO = oxygen consumption/AV oxygen difference
Oxygen consumption must be measured (can estimate w/ 125 mL/min/m^2, but inaccurate)
AV oxygen difference = Hb (g/dL) × 10 (dL/L) × 1.36 (mL O_2/g of Hb) × (S_aO_2 − $S_{MV}O_2$)

- S_aO_2 is measured in any arterial sample (usually 93–98%)
- $S_{MV}O_2$ (mixed venous O_2) is measured in RA, RV, or PA (assuming no shunt) (nl ~75%)

$$\therefore \textbf{Cardiac output (L/min)} = \frac{\text{Oxygen consumption}}{\text{Hb (g/dL)} \times 13.6 (S_aO_2 - S_vO_2)}$$

Assessment of RV function (*Circ* 2017;136:314)

PAPi = Pulmonary artery pulsatility index = [PA systolic – PA diastolic]/RA pressure
≤0.9 predicts RV failure in acute MI; <1.85 predicts RV failure after LVAD

Shunts

$$Q_p = \frac{\text{Oxygen consumption}}{\text{Pulm. vein } O_2 \text{ sat} - \text{Pulm. artery } O_2 \text{ sat}} \quad (\text{if no R} \rightarrow \text{L shunt, PV } O_2 \text{ sat} \approx S_aO_2)$$

$$Q_s = \frac{\text{Oxygen consumption}}{S_aO_2 - \text{mixed venous } O_2 \text{ sat}} \quad (MVO_2 \text{ drawn proximal to potential L} \rightarrow \text{R shunt})$$

$$\frac{Q_p}{Q_s} = \frac{S_aO_2 - \text{MV } O_2 \text{ sat}}{\text{PV } O_2 \text{ sat} - \text{PA } O_2 \text{ sat}} = \frac{S_aO_2 - \text{MV } O_2 \text{ sat}}{S_aO_2 - \text{PA } O_2 \text{ sat}} \quad (\text{if only L} \rightarrow \text{R and no R} \rightarrow \text{L shunt})$$

Valve equations

Simplified Bernoulli: Pressure gradient (∇P) = 4 × v^2 (where v = peak flow velocity)

Continuity (conservation of flow): $\text{Area}_1 \times \text{Velocity}_1 = A_2 \times V_2$ (where 1 & 2 different points)

$$\text{or AVA (unknown)} = A_{\text{LV outflow tract}} \times \left(\frac{V_{LVOT}}{V_{AoV}} \right) \quad (\text{all of which can be measured on echo})$$

$$\text{Gorlin equation: Valve area} = \frac{\text{CO} / (\text{DEP or SEP}) \times \text{HR}}{44.3 \times \text{constant} \times \sqrt{\text{mean} \nabla P}} \quad (\text{constant} = 1 \text{ for AS, } 0.85 \text{ for MS})$$

$$\text{Hakki equation: Valve area} \approx \frac{\text{CO}}{\sqrt{\text{peak instantaneous} \nabla P}}$$

Chest Imaging (CXR & CT) Patterns		
Pattern	**Pathophysiology**	**Ddx**
Consolidation	Radiopaque material in air space & interstitium patent airway → "air bronchograms"	*Acute:* water **(pulm. edema)**, pus **(PNA), blood** *Chronic:* neoplasm (BAC, lymphoma), aspiration, inflammatory (COP, eosinophilic PNA), PAP, granuloma (TB/fungal, alveolar sarcoid)
Ground glass (CT easier than CXR)	Interstitial thickening or partial filling of alveoli (but vessels visible)	*Acute:* pulm. edema, infxn (PCP, viral, resolving bact. PNA) Chronic: ILD w/o fibrosis: acute hypersens., DIP/RB, PAP w/ fibrosis: IPF
Septal lines Kerley A & B	Radiopaque material in septae	**Cardiogenic pulm. edema**, interstitial PNA viral, mycoplasma, lymphangitic tumor
Reticular	Lace-like net (ILD)	**ILD** (esp. IPF, CVD, bleomycin, asbestos)
Nodules	Tumor Granulomas Abscess	*Cavitary:* **Primary or metastatic cancer**, **TB** (react. or miliary), **fungus**, Wegener's, RA **septic emboli**, PNA *Noncavitary:* any of above + **sarcoid**, hypersens. pneum., HIV, Kaposi's sarcoma
Wedge opac.	Peripheral infarct	**PE**, cocaine, angioinv. aspergillus, Wegener's
Tree-in-bud (best on CT)	Inflammation of small airways	**Bronchopneumonia**, endobronchial TB/MAI, viral PNA, aspiration, ABPA, CF, asthma, COP
Hilar fullness	↑ LN or pulm. arteries	**Neoplasm** (lung, mets, lymphoma) **Infxn** (AIDS); **Granuloma** (sarcoid/TB/fungal) Pulmonary hypertension
Upper lobe	n/a	**TB**, fungal, sarcoid, hypersens. pneum., CF, XRT
Lower lobe	n/a	**Aspiration**, bronchiect., IPF, RA, SLE, asbestos
Peripheral	n/a	COP, IPF & DIP, eos PNA, asbestosis

CXR in heart failure

- ↑ cardiac silhouette (in systolic dysfxn, not in diastolic)
- Pulmonary venous hypertension: cephalization of vessels (vessels size > bronchi in upper lobes), peribronchial cuffing (fluid around bronchi seen on end → small circles), Kerley B lines (horizontal 1- to 2-cm lines at bases), ↑ vascular pedicle width, loss of sharp vascular margins, pleural effusions (~75% bilateral)
- Pulmonary edema: ranges from ground glass to consolidation; often dependent and central, sparing outer third ("bat wing" appearance)

Dead space = lung units that are ventilated but not perfused
Intrapulmonary shunt = lung units that are perfused but not ventilated

Alveolar gas equation: $P_AO_2 - \left[F_iO_2 \times (760 - 47)\right] - \frac{P_aCO_2}{R}$ (where R ≈ 0.8)

$$P_AO_2 = 150 - \frac{P_aCO_2}{0.8} \text{ (on room air)}$$

A-a gradient = $P_AO_2 - P_aO_2$ [normal A-a gradient ≈ 4 + (age/4)]
Minute ventilation (V_E) = tidal volume (V_T) × respiratory rate (RR) (nl 4–6 L/min)
Tidal volume (V_T) = alveolar space (V_A) + dead space (V_D)

Fraction of tidal volume that is dead space $\left(\frac{V_D}{V_T}\right) = \frac{P_aCO_2 - P_{expired}CO_2}{P_aCO_2}$

$$PaCO_2 = k \times \frac{CO_2 \text{ Production}}{\text{Alveolar ventilation}} = k \times \frac{\dot{V}CO_2}{RR \times (V_T - V_D)}$$

Gastroenterology

Modified Child–Turcotte–Pugh (CPS) Scoring System			
	Points Scored		
	1	**2**	**3**
Ascites	None	Easily controlled	Poorly controlled
Encephalopathy	None	Grade 1 or 2	Grade 3 or 4
Bilirubin (mg/dL)	<2	2–3	>3
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
PT (sec >control) or INR	<4 <1.7	4–6 1.8–2.3	>6 >2.3
Classification			
	A	**B**	**C**
Total points	5–6	7–9	10–15
1-y survival	100%	80%	45%

Nephrology

Anion gap (AG) = Na − (Cl + HCO_3) (normal = [alb] × 2.5; typically 12 ± 2 mEq)
Delta-delta (ΔΔ) = [Δ AG (ie, calc. AG − expected)/Δ HCO_3 (ie, 24 − measured HCO_3)]
Urine anion gap (UAG) = (U_{Na} + U_K) − U_{Cl}

Calculated osmoles $= (2 \times Na) + \left(\frac{glc}{18}\right) + \left(\frac{BUN}{2.8}\right) + \left(\frac{EtOH}{4.6}\right)$

Osmolal gap (OG) = measured osmoles – calculated osmoles (normal <10)

Estimated creatinine clearance $= \frac{[140 - \text{age (yr)}] \times \text{wt (kg)}}{\text{serum Cr (mg/dL)} \times 72}$ (× 0.85 in women)

Fractional excretion of Na $(FE_{Na}, \%) = \left[\frac{\frac{U_{Na}\,(mEq/L)}{P_{Na}\,(mEq/L)} \times 100\%}{\frac{U_{Cr}\,(mg/mL)}{P_{Cr}\,(mg/dL)} \times 100\ (mL/dL)}\right] = \frac{\frac{U_{Na}}{P_{Na}}}{\frac{U_{Cr}}{P_{Cr}}}$

Corrected Na in hyperglycemia

estimate in all Pts: corrected Na = measured Na + $\left[2.4 \times \frac{(\text{measured glc} - 100)}{100}\right]$

however, Δ in Na depends on glc (*Am J Med* 1999;106:399)
Δ is 1.6 mEq per each 100 mg/dL ↑ in glc ranging from 100 to 440
Δ is 4 mEq per each 100 mg/dL ↑ in glc beyond 440

Total body water (TBW) = 0.60 × IBW (× 0.85 if female and × 0.85 if elderly)

Free H_2O deficit $= \text{TBW} \times \left(\frac{[Na]_{serum} - 140}{140}\right) \approx \left(\frac{[Na]_{serum} - 140}{3}\right)$ (in 70 kg Pt)

Trans-tubular potassium gradient (TTKG) $= [U_K/P_K]/[U_{Osm}/P_{Osm}]$

Hematology

Peripheral Smear Findings (also see Photo Inserts)	
Feature	**Abnormalities and Diagnoses**
Size	normocytic vs. microcytic vs. macrocytic → see below
Shape	**Anisocytosis** → unequal RBC size; **poikilocytosis** → irregular RBC shape acanthocytes = **spur** cells (irregular sharp projections) → liver disease **Bite** cells (removal of Heinz bodies by phagocytes) → G6PD deficiency echinocytes = **burr** cells (even, regular projections) → uremia, artifact **Pencil cell** → long, thin, hypochromic—very common in adv. iron deficiency **Rouleaux** → hyperglobulinemia (eg, multiple myeloma) **Schistocytes**, helmet cells → MAHA (eg, DIC, TTP/HUS), mechanical valve **Spherocytes** → HS, AIHA; **sickle** cells → sickle cell anemia **Stomatocyte** → central pallor appears as curved slit → liver disease, EtOH **Target** cells → liver disease, hemoglobinopathies, splenectomy **Tear drop** cells = dacrocytes → myelofibrosis, myelophthisic anemia, megaloblastic anemia, thalassemia

Intra-RBC findings	**Basophilic stippling** (ribosomes) → abnl Hb, sideroblastic, megaloblastic **Heinz bodies** (denatured Hb) → G6PD deficiency, thalassemia **Howell–Jolly bodies** (nuclear fragments) → splenectomy or functional asplenia (eg, advanced sickle cell) **Nucleated** RBCs → hemolysis, extramedullary hematopoiesis
WBC findings	**Blasts** → leukemia, lymphoma; **Auer rods** → acute myelogenous leukemia **Hypersegmented** (>5 lobes) PMNs: megaloblastic anemia (B_{12}/folate def.) **Pseudo-Pelger–Huët anomaly** (bilobed nucleus, "pince-nez") → MDS **Toxic granules** (coarse, dark blue) and **Döhle bodies** (blue patches of dilated endoplasmic reticulum) → (sepsis, severe inflammation)
Platelet	**Clumping** → artifact, repeat plt count # → periph blood plt count ~10,000 plt for every 1 plt seen at hpf (100×) **Size** → MPV (mean platelet volume) enlarged in ITP

(*NEJM* 2005;353:498)

Heparin for Thromboembolism	
80 U/kg bolus 18 U/kg/h	
PTT	**Adjustment**
<40	bolus 5000 U, ↑ rate 300 U/h
40–49	bolus 3000 U, ↑ rate 200 U/h
50–59	↑ rate 150 U/h
60–85	no Δ
86–95	↓ rate 100 U/h
96–120	hold 30 min, ↓ rate 100 U/h
>120	hold 60 min, ↓ rate 150 U/h

(Modified from *Chest* 2008;133:141S)

- PTT q6h after every Δ ($t_{½}$ of heparin ~90 min) and then qd or bid once PTT is therapeutic
- CBC qd (to ensure Hct and plt counts are stable)

Warfarin Loading Nomogram					
Day	**INR**				
	<1.5	**1.5–1.9**	**2–2.5**	**2.6–3**	**>3**
1–3	5 mg (7.5 mg if >80 kg)		2.5–5 mg	0–2.5 mg	0 mg
4–5	10 mg	5–10 mg	0–5 mg		0–2.5 mg
6	Dose based on requirements over preceding 5 d				

(*Annals* 1997;126:133; *Archives* 1999;159:46) or, go to www.warfarindosing.org

Warfarin–heparin overlap therapy

- Indications: when failure to anticoagulate carries ↑ risk of morbidity or mortality (eg, DVT/PE, intracardiac thrombus)
- Rationale: (1) Half-life of factor VII (3–6 h) is shorter than half-life of factor II (60–72 h);
  ∴ warfarin can elevate PT *before achieving a true antithrombotic state*
  (2) Protein C also has half-life less than that of factor II;

∴ theoretical concern of *hypercoagulable state* before antithrombotic state

- Method: (1) Therapeutic PTT is achieved using heparin
  (2) Warfarin therapy is initiated
  (3) Heparin continued until INR therapeutic for ≥2 d and ≥4–5 d of warfarin (roughly corresponds to ~2 half-lives of factor II or a reduction to ~25%)

Common Warfarin–Drug Interactions

Drugs that ↑ PT	Drugs that ↓ PT
Amiodarone Antimicrobials: erythromycin, ? clarithro, ciprofloxacin, MNZ, sulfonamides Antifungals: azoles Acetaminophen, cimetidine, levothyroxine	Antimicrobials: rifampin CNS: barbiturates, carbamazepine, phenytoin (initial transient ↑ PT) Cholestyramine

Endocrinology

Examples of Various Cosyntropin Stimulation Test Results

0′	30′	60′	Interpretation (using modern cortisol assays)
5.3	12.5	17.2	Normal stimulation test
0.5	13.3	21.1	Acute central AI (eg, apoplexy or CNS bleed). Can look normal.
1.2	1.5	2.0	1° AI (eg, Addison's or adrenal bleed). Flat or minimal stim.
0.8	10.0	18.7	Exogenous glucocorticoids: low initial value but stims > threshold
5.3	7.2	8.9	Chronic 2° AI: some cortisol production and stim, but evidence of adrenal atrophy
6.7	17.5	14.2	"Early peak" (fast metab): ~5% of Pts peak at 30′ rather than 60′
6.3	10.5	13.2	Equivocal test. Can occur due to mild AI, acute illness, liver disease, low cortisol binding protein, renal disease, etc.

Neurology

Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar)					
Assign points for each of the 10 criteria; each criterion is scored 0–7, except orientation, which is scored 0–4; add points to calculate score					
Points	**Anxiety**	**Agitation**	**Tremor**	**HA**	**Orientation**
0	None	None	None	None	Oriented
1		Somewhat	Not visible, but felt at fingertips	Very mild	Cannot do serial additions
2				Mild	Disorient. by ?2 d
3				Moderate	Disorient. by >2 d
4	Guarded	Restless	Moderate w/ hands extended	Mod–severe	Disoriented to person or place
5				Severe	n/a
6				Very severe	n/a
7	Panic	Pacing or thrashing	Severe	Extremely severe	n/a
Points	**N/V**	**Sweats**	**Auditory Hallucinations**	**Visual Halluc.**	**Tactile Disturb**
0	None	None	None	None	None
1		Moist palms	Very mild	Very mild photosens.	Very mild paresthesias
2			Mild	Mild photosens.	Mild paresth.
3			Moderate	Mod photosens.	Mod paresth.
4	Intermit. w/ dry heaves	Beads	Mod–severe	Mod–severe visual halluc.	Mod–severe hallucinations
5			Severe	Severe	Severe
6			Very severe	Very severe	Very severe
7	Constant	Drenching	Cont.	Continuous	Continuous
SCORE: <8 none to minimal withdrawal; 8–15 mild; 16–20 moderate; >20 severe					

Other

Ideal body weight (IBW) = [50 kg (men) or 45.5 kg (women)] + 2.3 kg/inch over 5 feet

Body surface area (BSA, m^2) $= \sqrt{\frac{\text{height (cm)} \times \text{weight (kg)}}{3600}}$

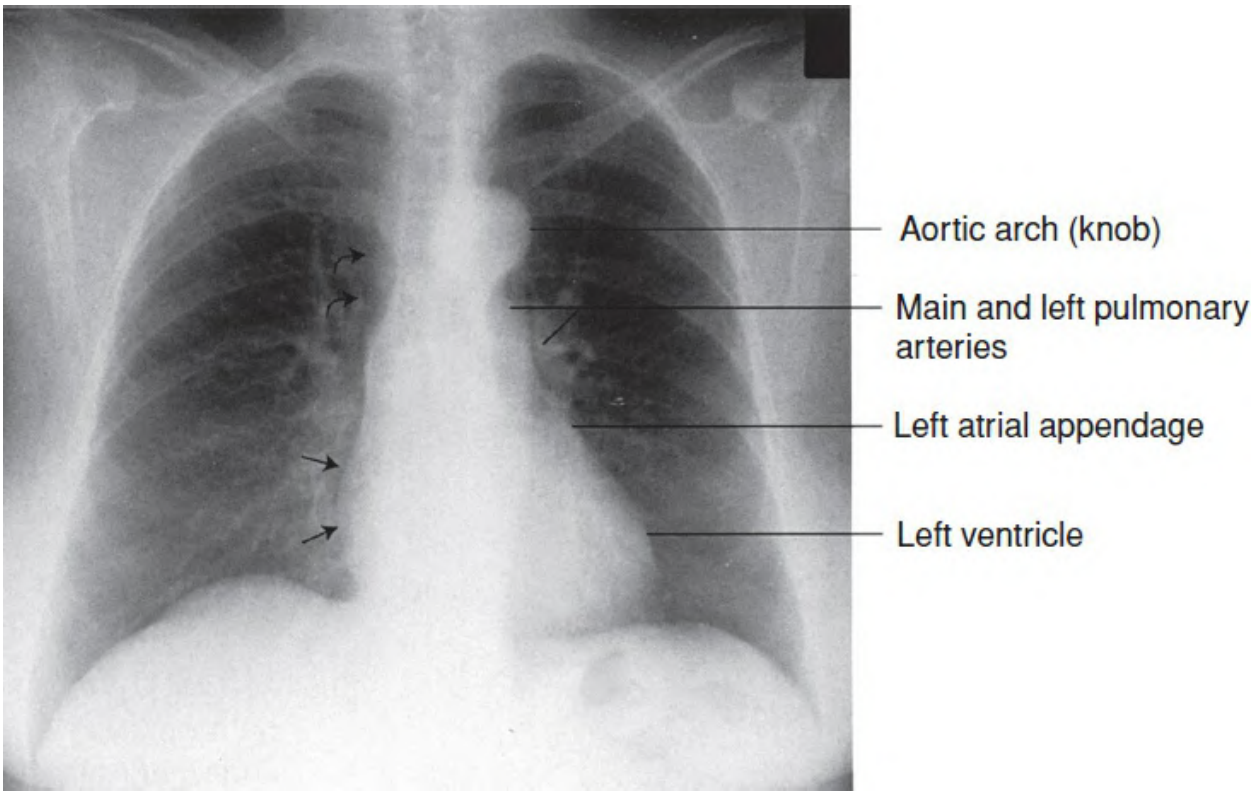
		Disease	
		present	absent
Test	$\oplus$	a (true $\oplus$)	b (false $\oplus$)
	$\ominus$	c (false $\ominus$)	d (true $\ominus$)

Sensitivity $= \frac{\text{true positives}}{\text{all diseased}} = \frac{a}{a+c}$ **Specificity** $= \frac{\text{true negatives}}{\text{all healthy}} = \frac{d}{b+d}$

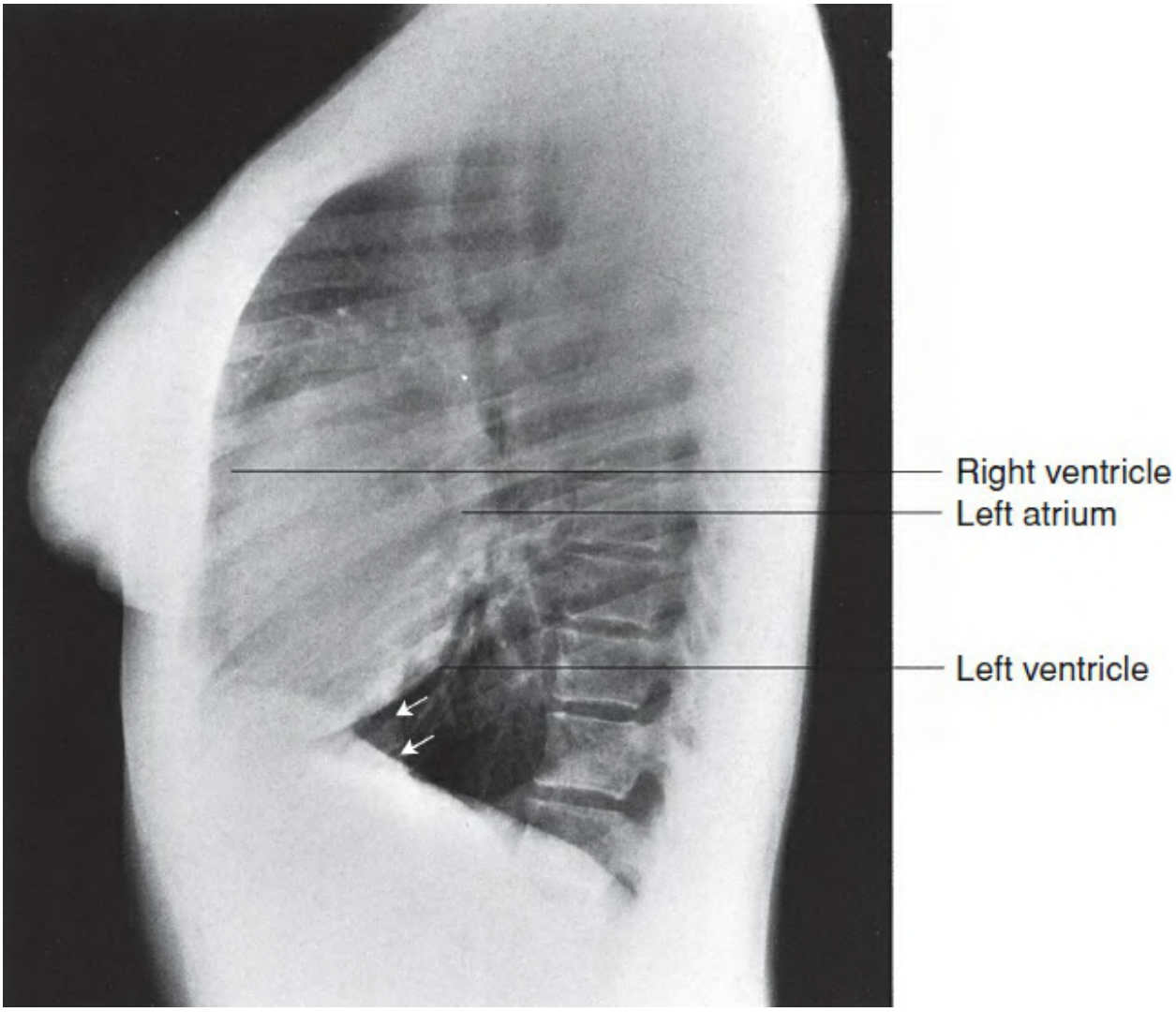
$\oplus$ **Predictive value** $= \frac{\text{true positives}}{\text{all diseased}} = \frac{a}{a+b}$

$\ominus$ **Predictive value** $= \frac{\text{true negatives}}{\text{all healthy}} = \frac{d}{c+d}$

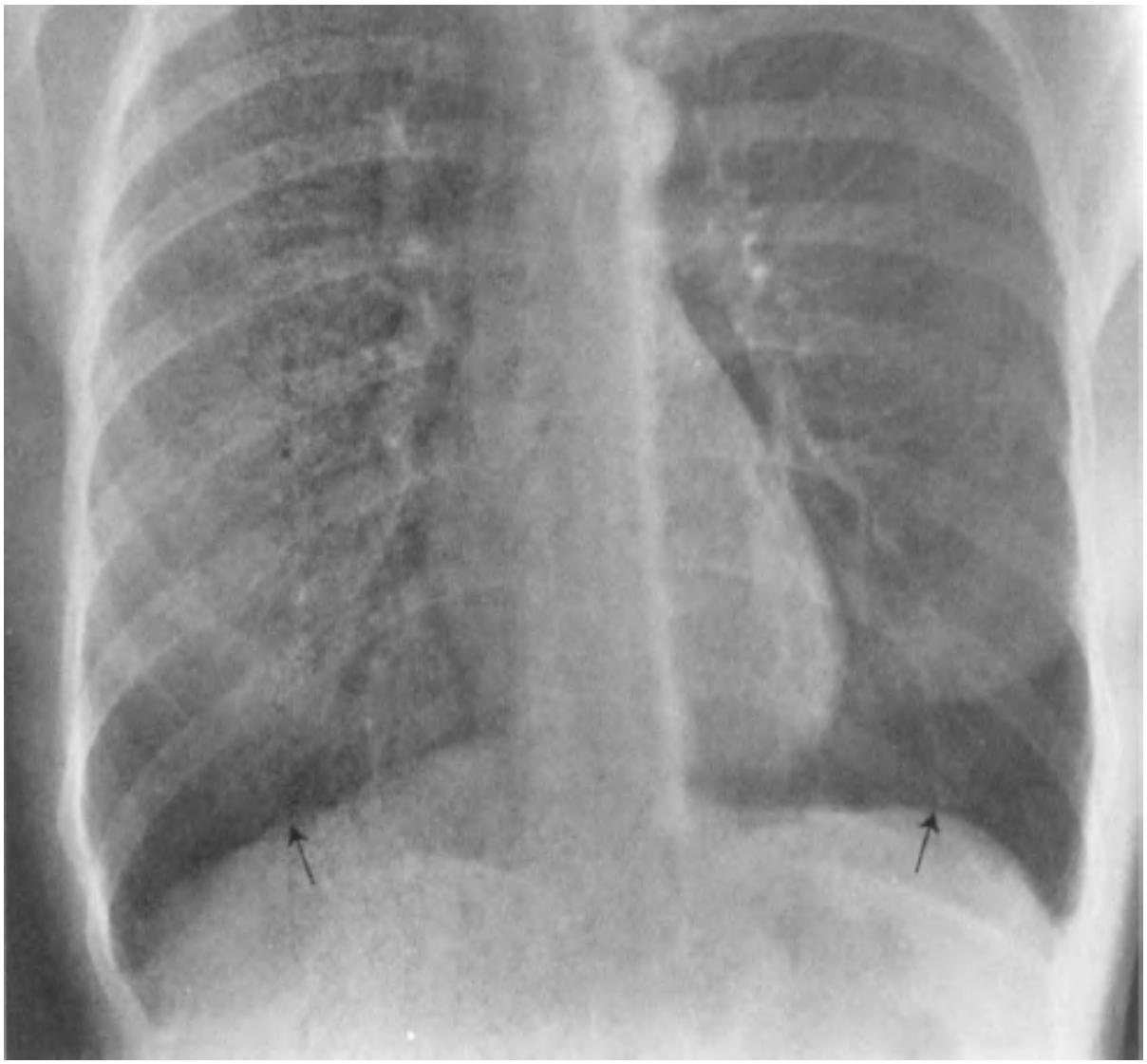
NOTES



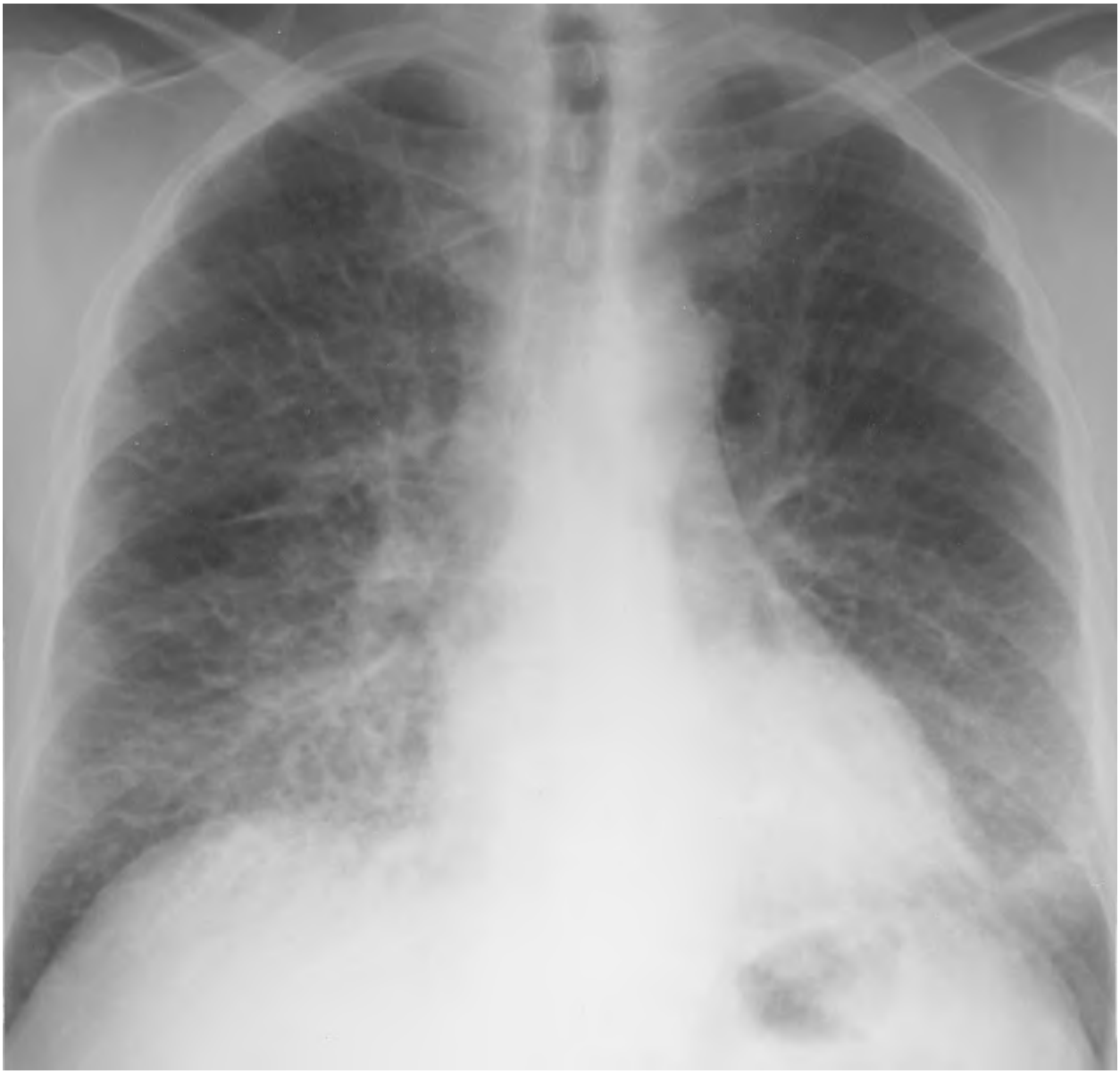
1 Normal PA CXR. The convex right cardiac border is formed by the right atrium (straight arrows), and the curved arrows indicate the location of the superior vena cava. The left cardiac and great vessels border what might be considered as 4 skiing moguls. From cephalad to caudad, the moguls are the aortic arch, the main and left pulmonary arteries, the left atrial appendage, and the left ventricle. (Reprinted with permission from *Radiology 101*, 3rd ed, 2010.)



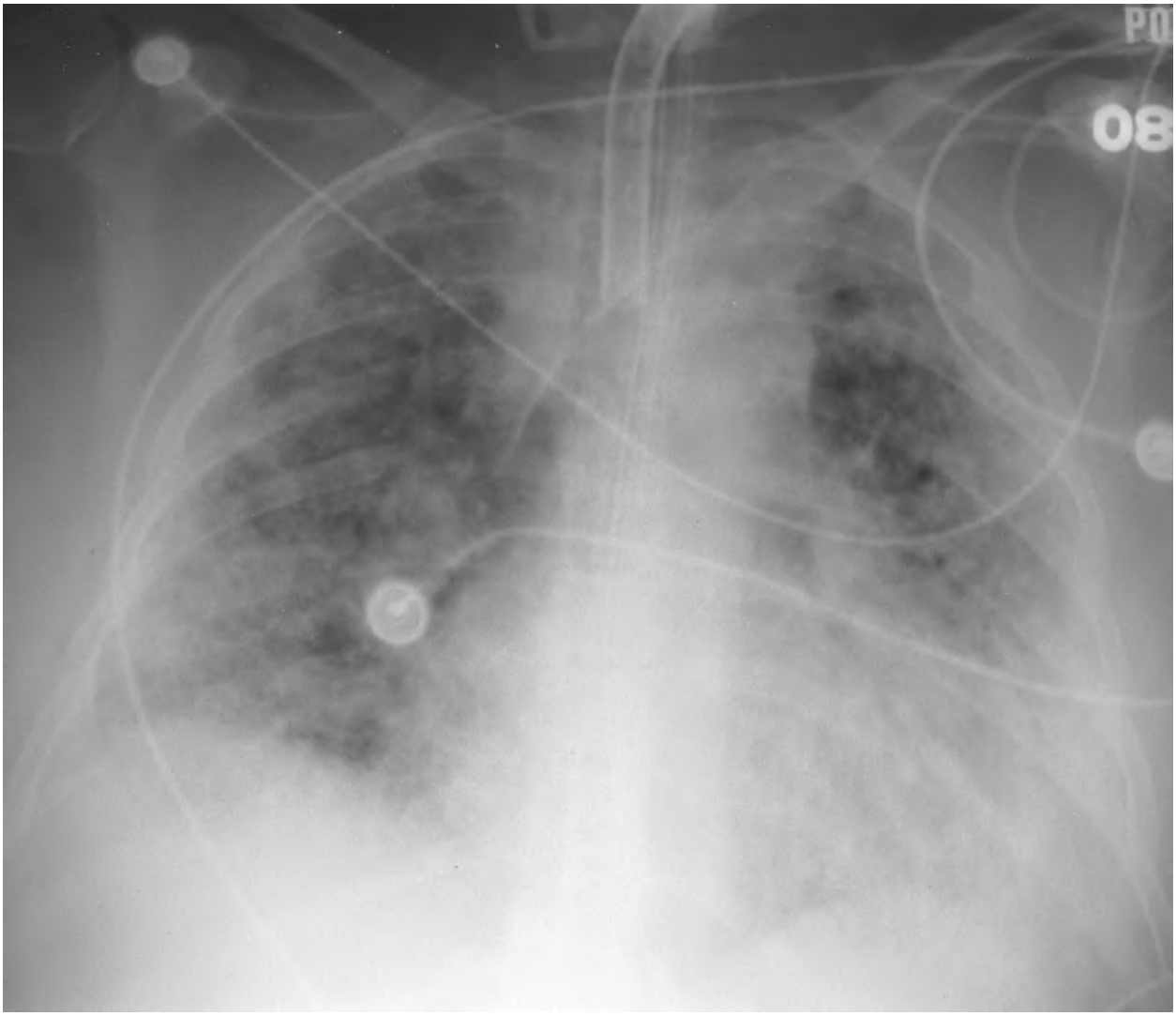
2 Normal lateral CXR. (Reprinted with permission from *Radiology 101*, 3rd ed, 2010.)



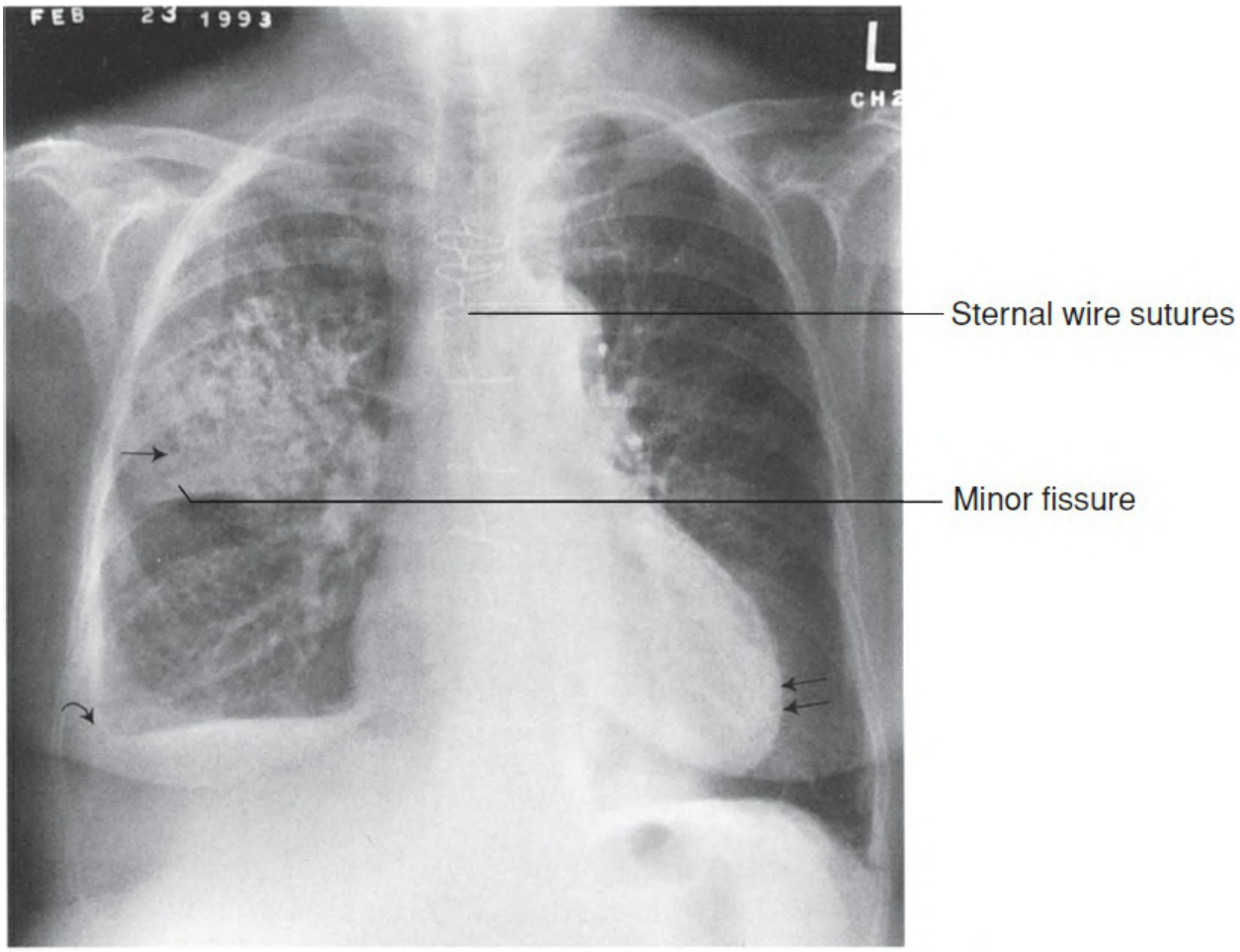
3 COPD: with hyperlucent, overinflated lungs and flat diaphragms. (Reprinted with permission from *Radiology 101*, 3rd ed, 2010.)



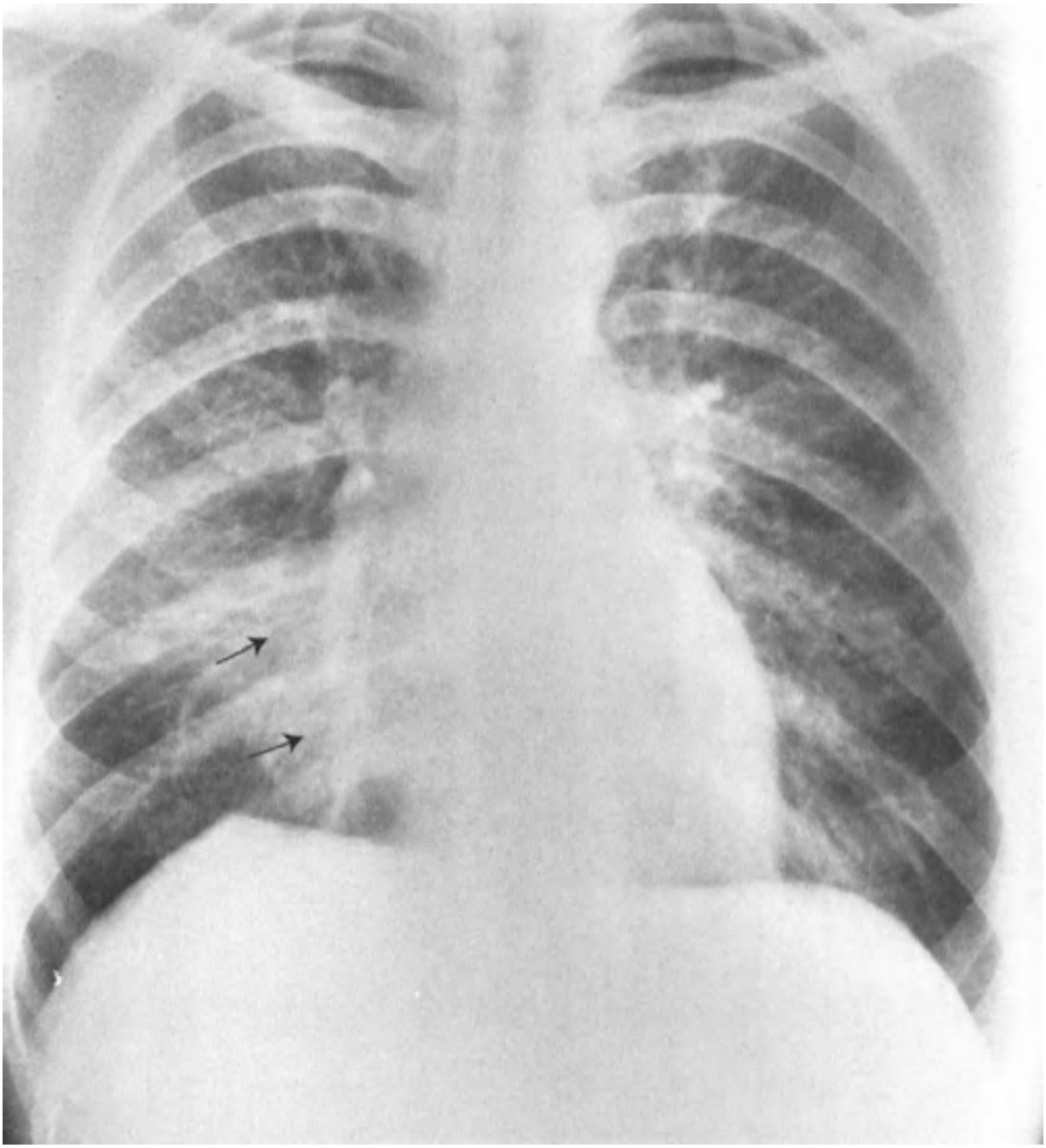
4 Interstitial pulmonary edema: with Kerley A, B, and C lines and cephalization of the vascular markings. (Reprinted with permission from *Fundamentals of Diagnostic Radiology,* 3rd ed, 2007.)



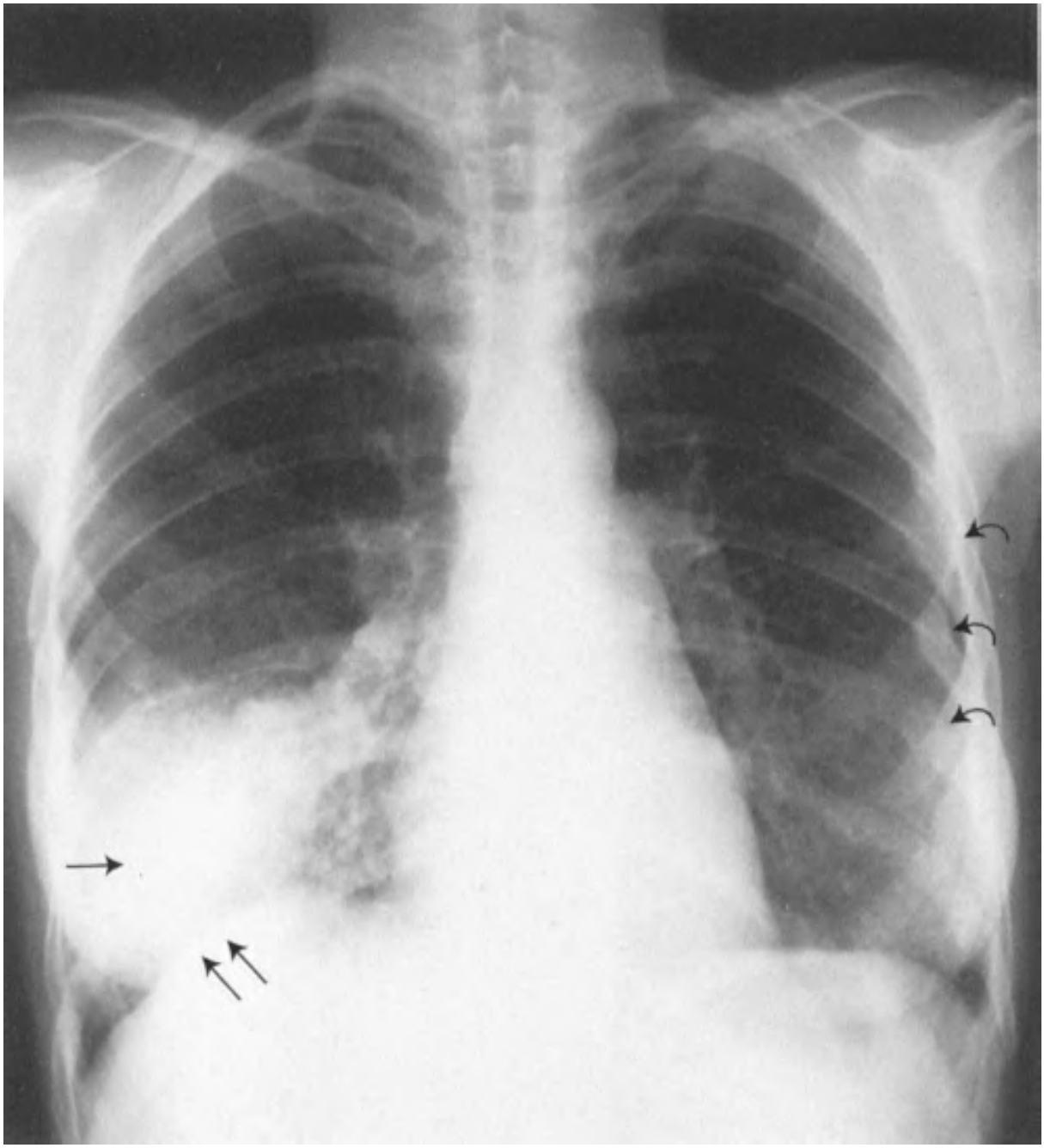
5 Alveolar pulmonary edema. (Reprinted with permission from *Fundamentals of Diagnostic Radiology,* 3rd ed, 2007.)



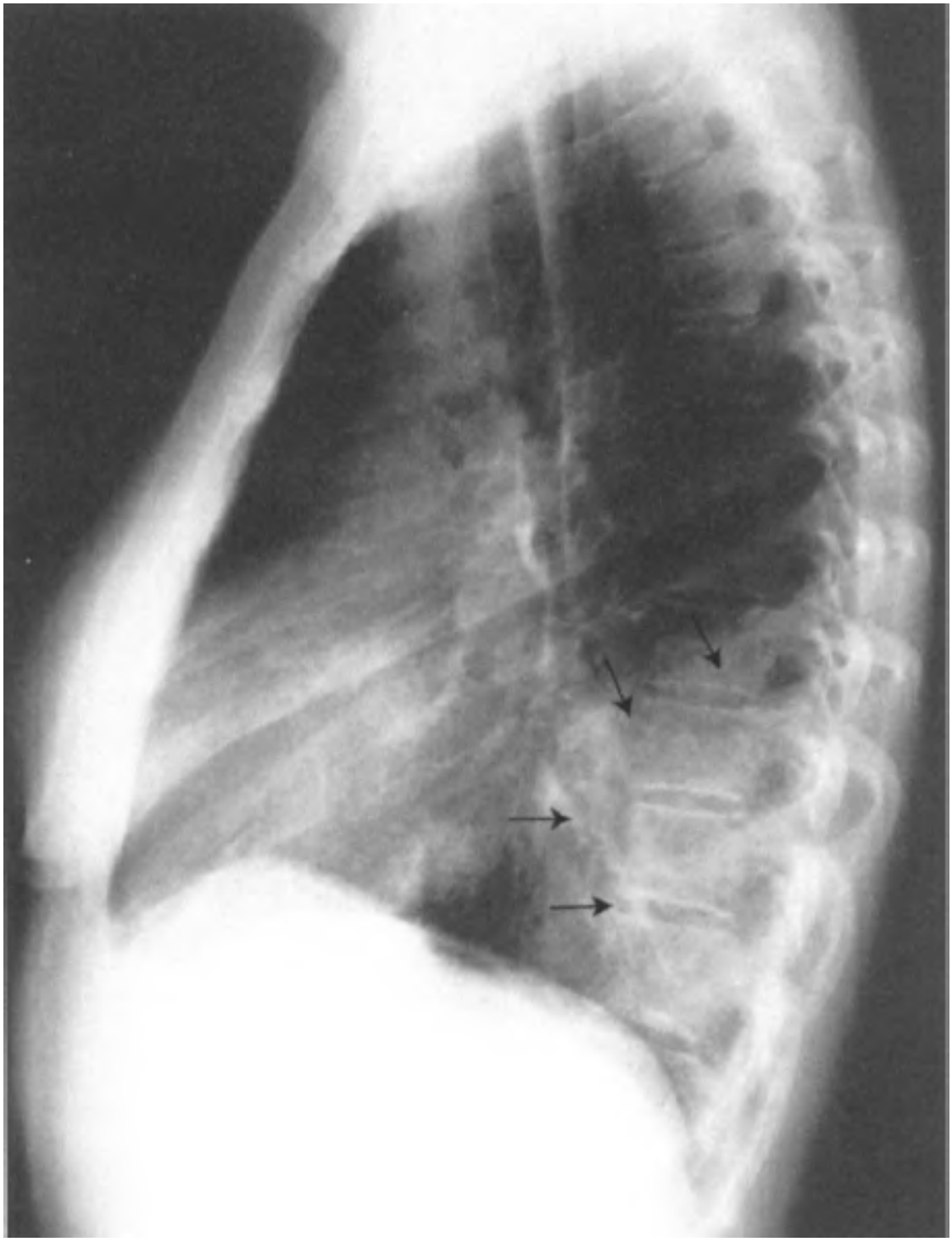
6 Right upper lobe pneumonia. (Reprinted with permission from *Radiology 101*, 3rd ed, 2010.)



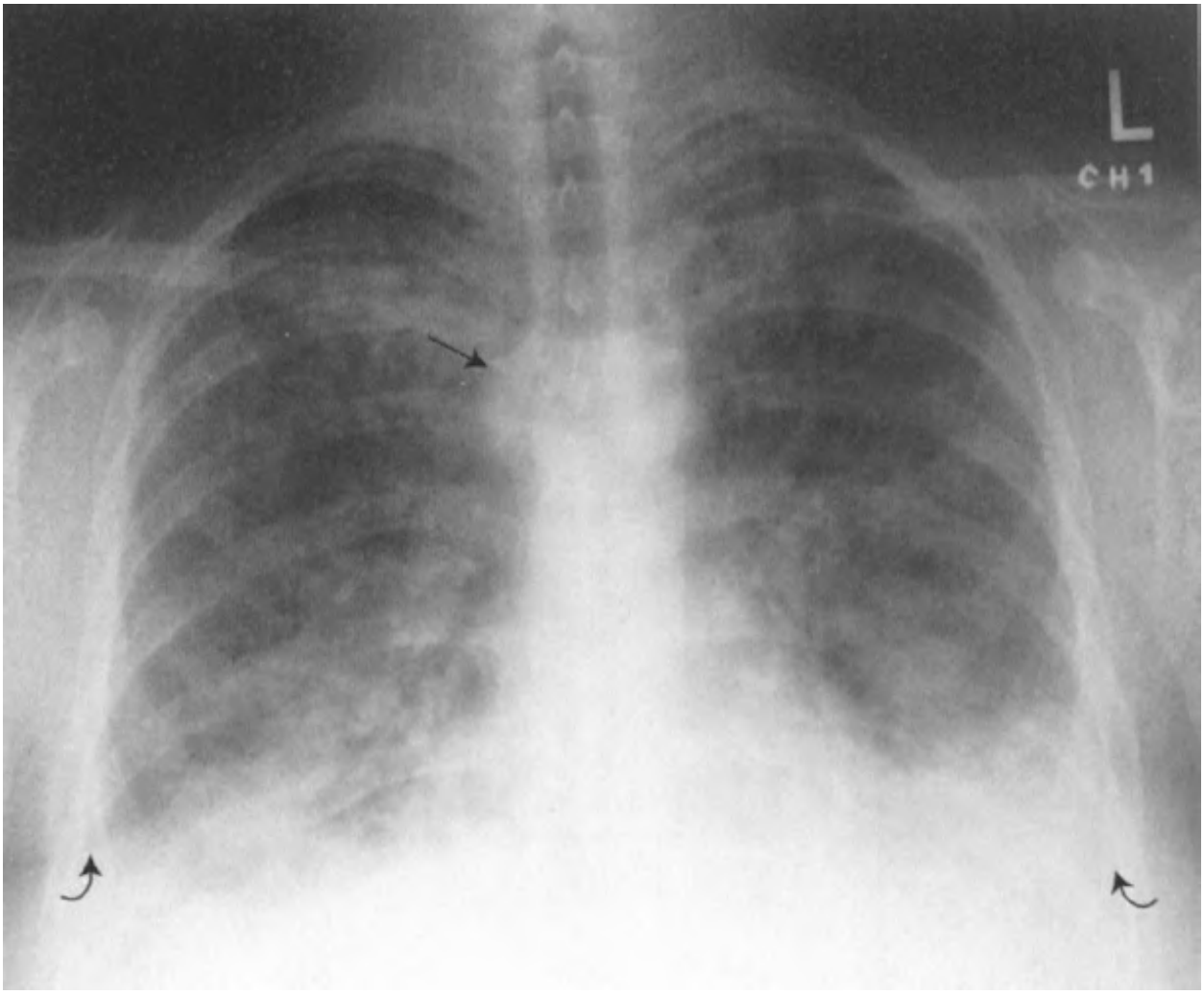
7 Right middle lobe pneumonia. (Reprinted with permission from *Radiology 101*, 3rd ed, 2010.)



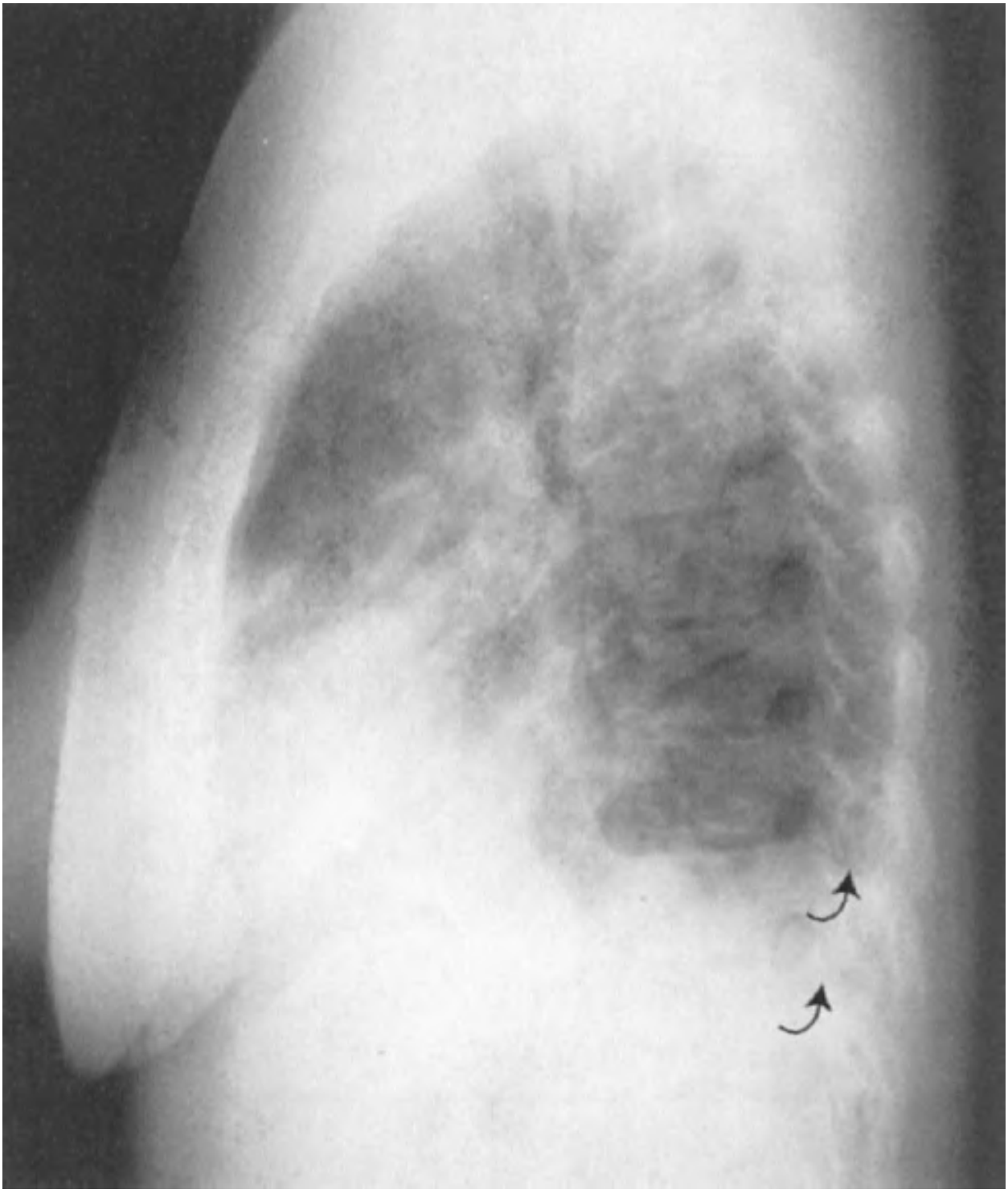
8 Right lower lobe pneumonia (PA). (Reprinted with permission from *Radiology 101*, 3rd ed, 2010.)



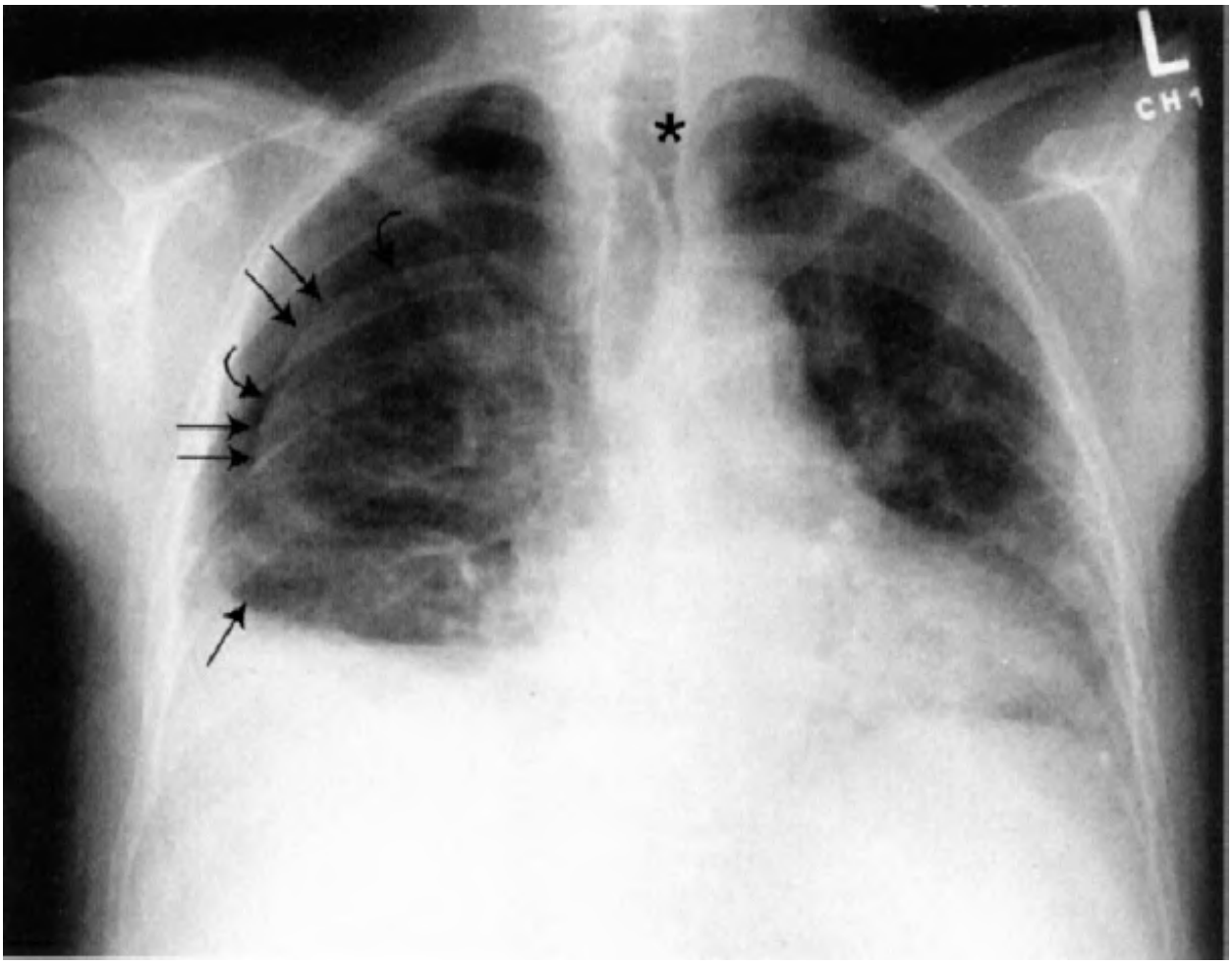
9 Right lower lobe pneumonia (lateral). (Reprinted with permission from *Radiology 101*, 3rd ed, 2010.)



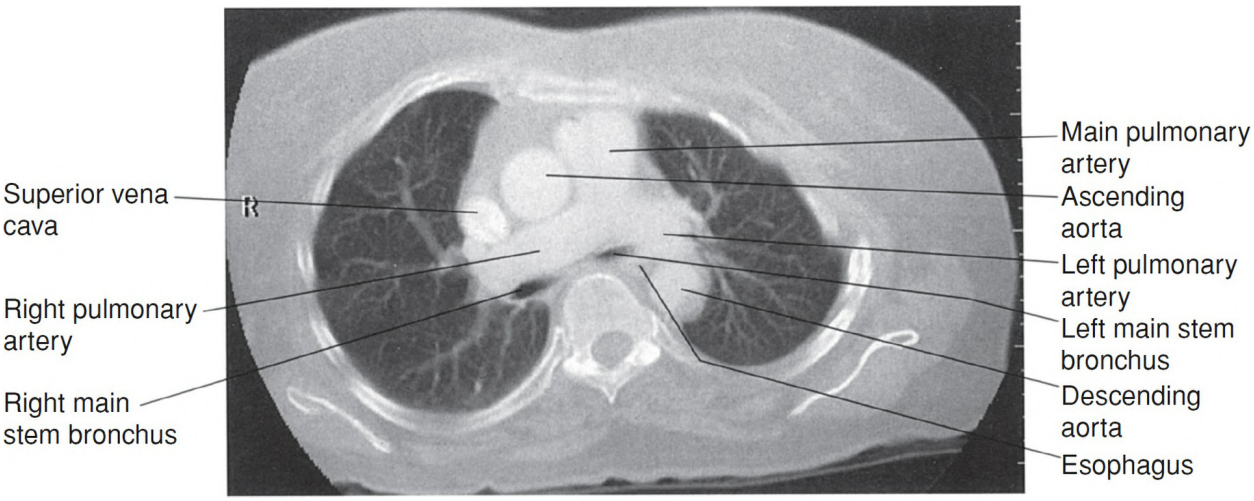
10 Bilateral pleural effusions (curved arrows) and enlarged azygous vein (straight arrow). (PA). (Reprinted with permission from *Radiology 101*, 3rd ed, 2010.)



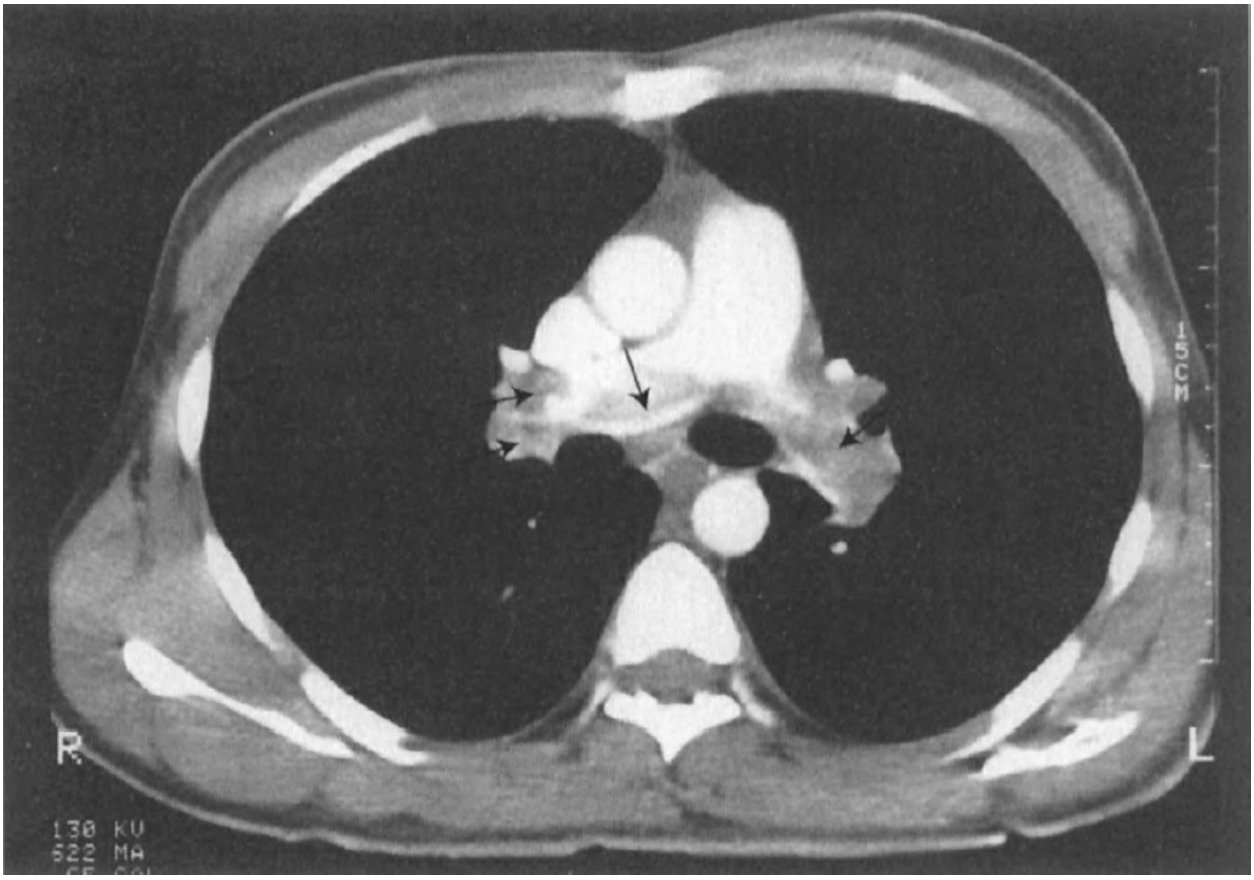
11 Bilateral pleural effusions (curved arrows) (lateral). (Reprinted with permission from *Radiology 101*, 3rd ed, 2010.)



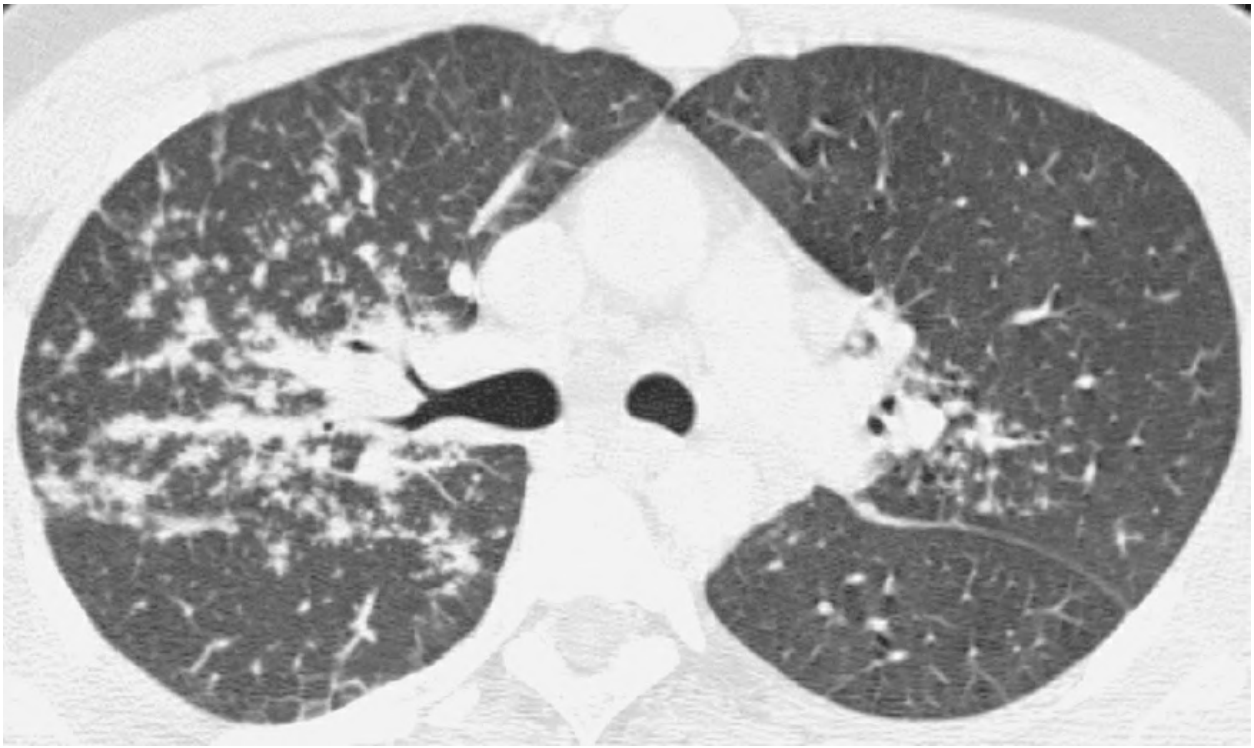
12 Pneumothorax. (Reprinted with permission from *Radiology 101*, 3rd ed, 2010.)



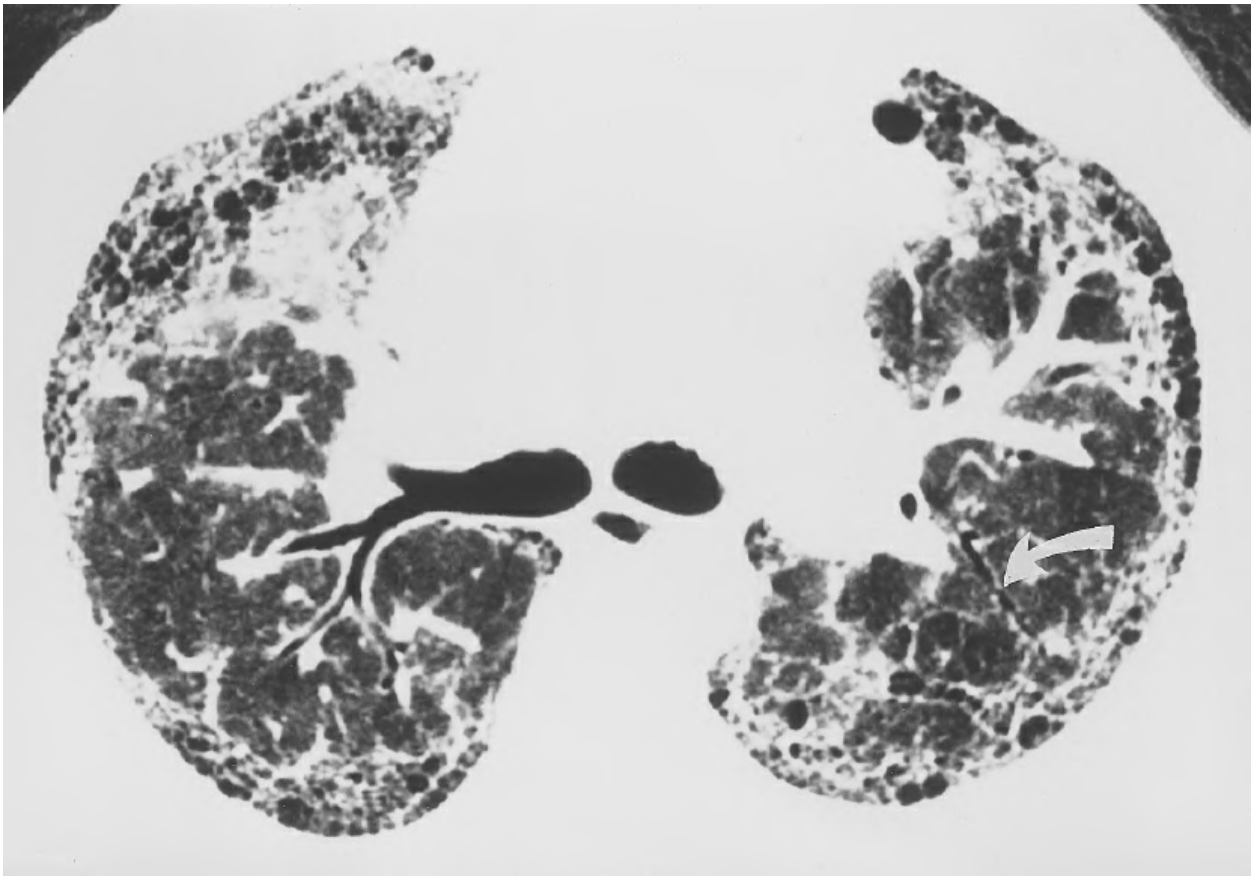
13 Normal chest CT at level of pulmonary arteries (parenchymal windows). (Reprinted with permission from *Radiology 101*, 3rd ed, 2010.)



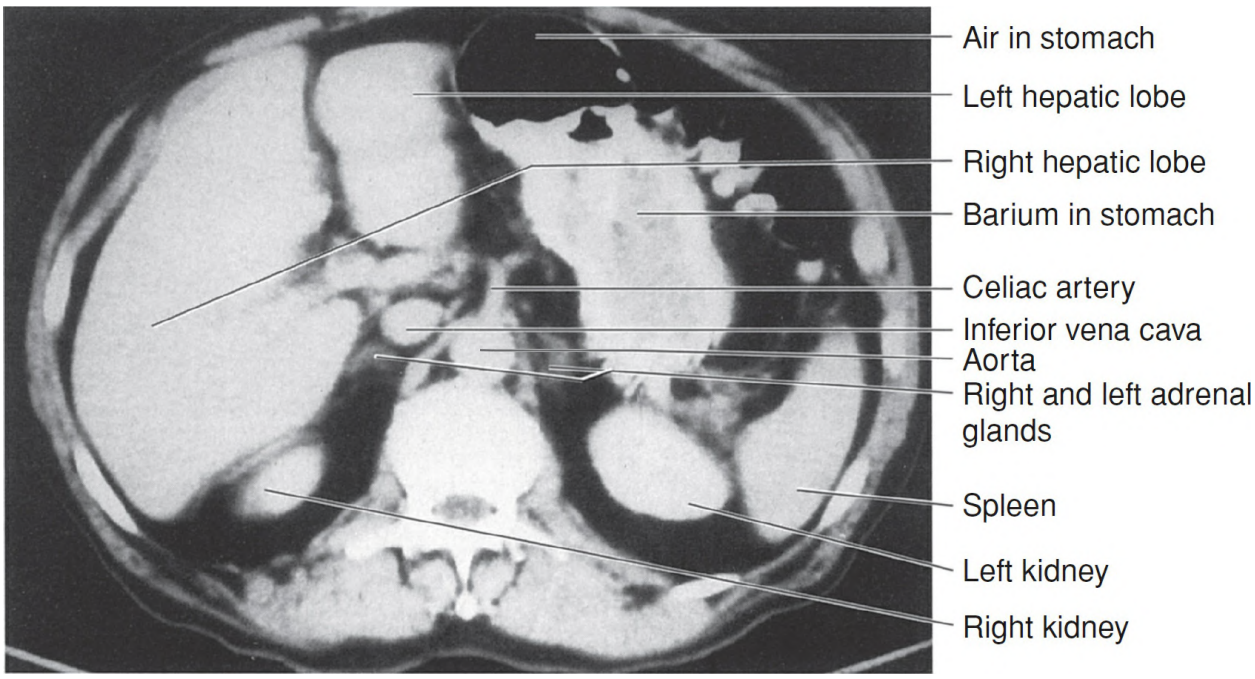
14 Bilateral PE (mediastinal windows). (Reprinted with permission from *Radiology 101*, 3rd ed, 2010.)



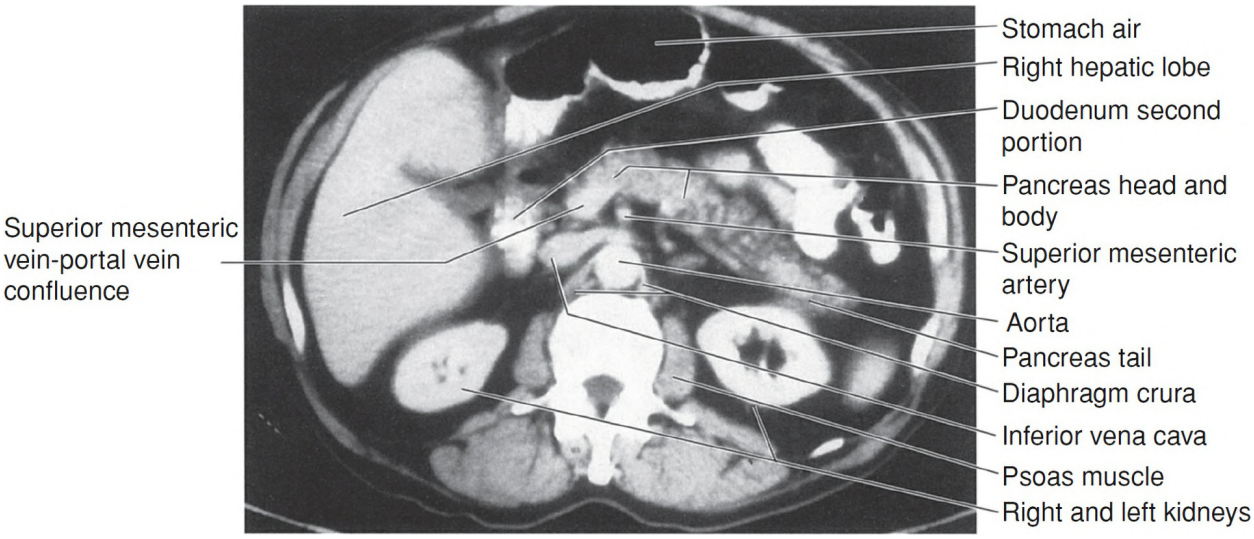
15 Sarcoidosis with perilymphatic nodules. (Reprinted with permission from *Fundamentals of Diagnostic Radiology,* 3rd ed, 2007.)



16 Idiopathic pulmonary fibrosis. (Reprinted with permission from *Fundamentals of Diagnostic Radiology,* 3rd ed, 2007.)

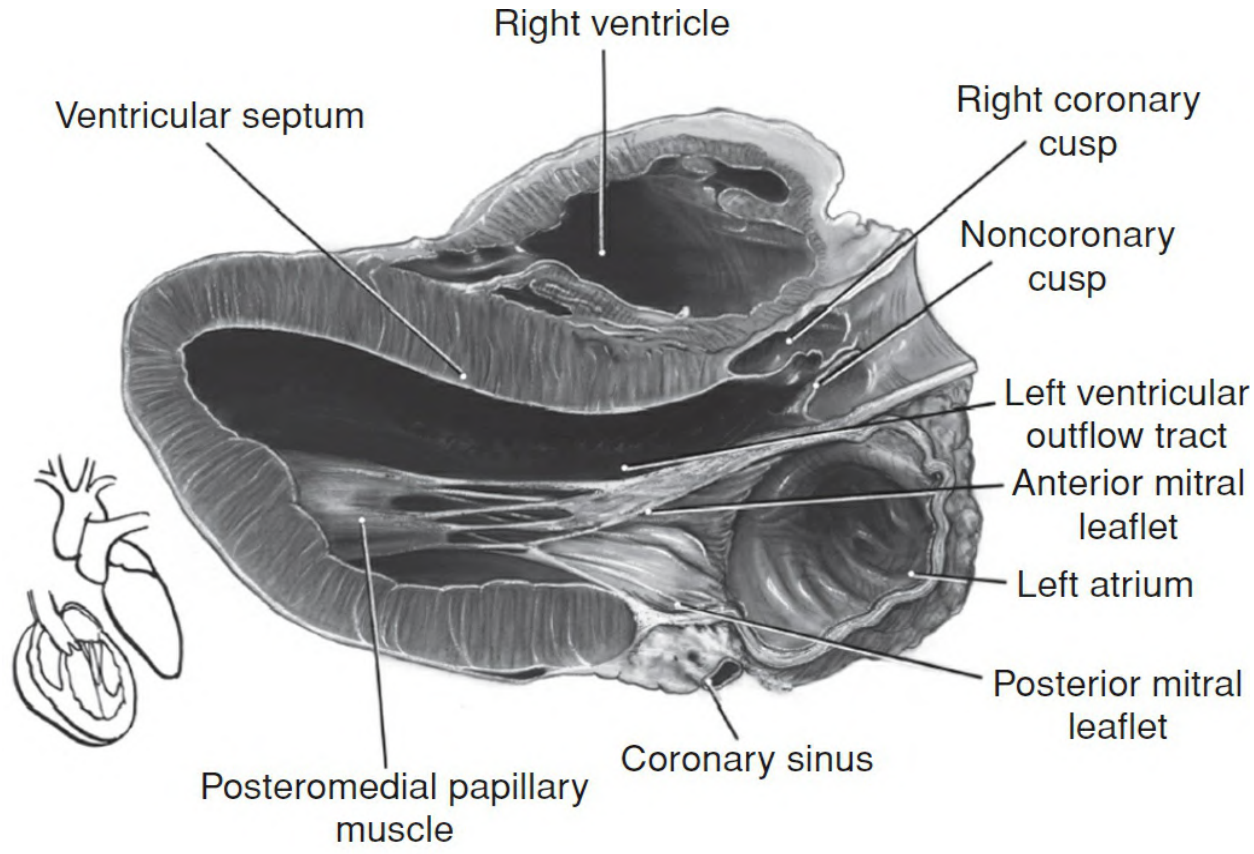


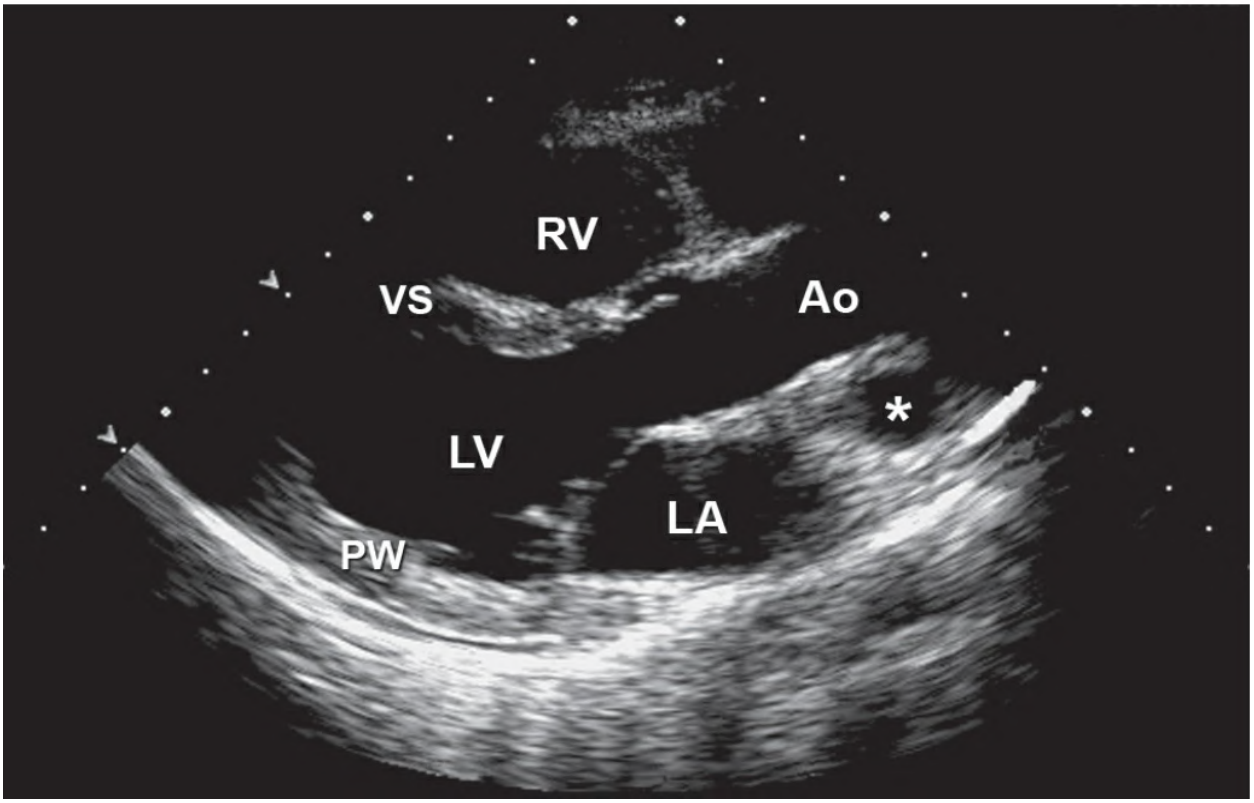
17 Normal abdomen CT at level of liver & spleen. (Reprinted with permission from *Radiology 101*, 3rd ed, 2010.)



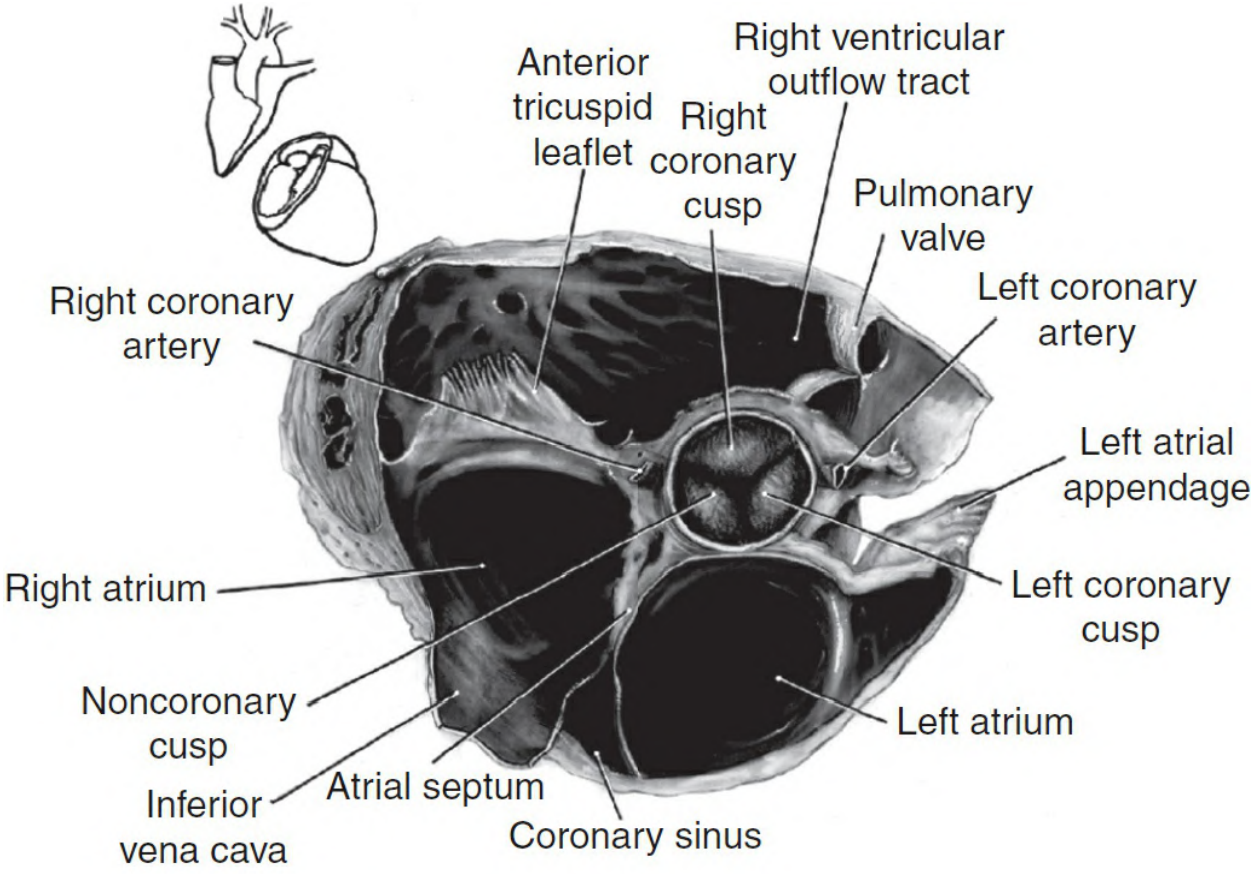
18 Normal abdomen CT at level of pancreas. (*Reprinted with permission from Radiology 101*, 3rd ed, 2010.)

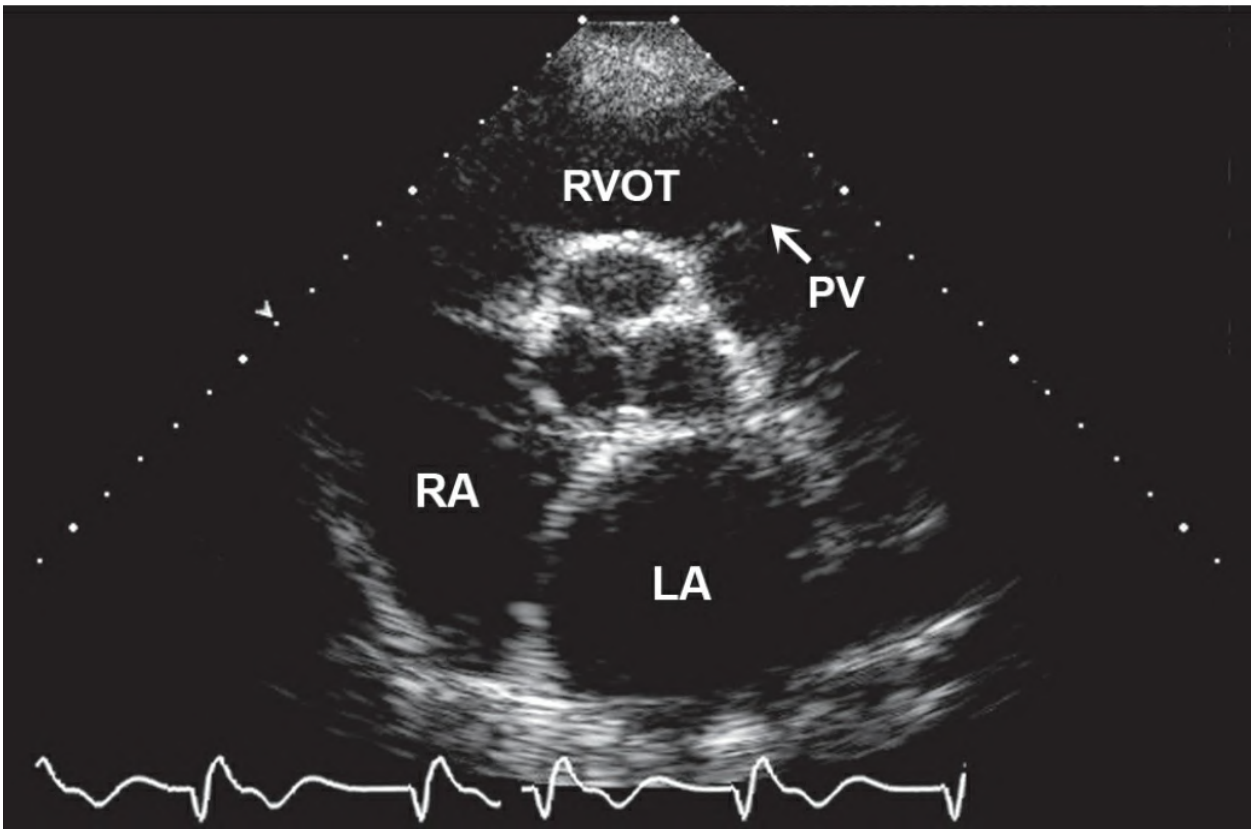
Echocardiography


Right ventricle
Ventricular septum
Right coronary cusp
Noncoronary cusp
Left ventricular outflow tract
Anterior mitral leaflet
Left atrium
Posterior mitral leaflet
Coronary sinus
Posteromedial papillary muscle

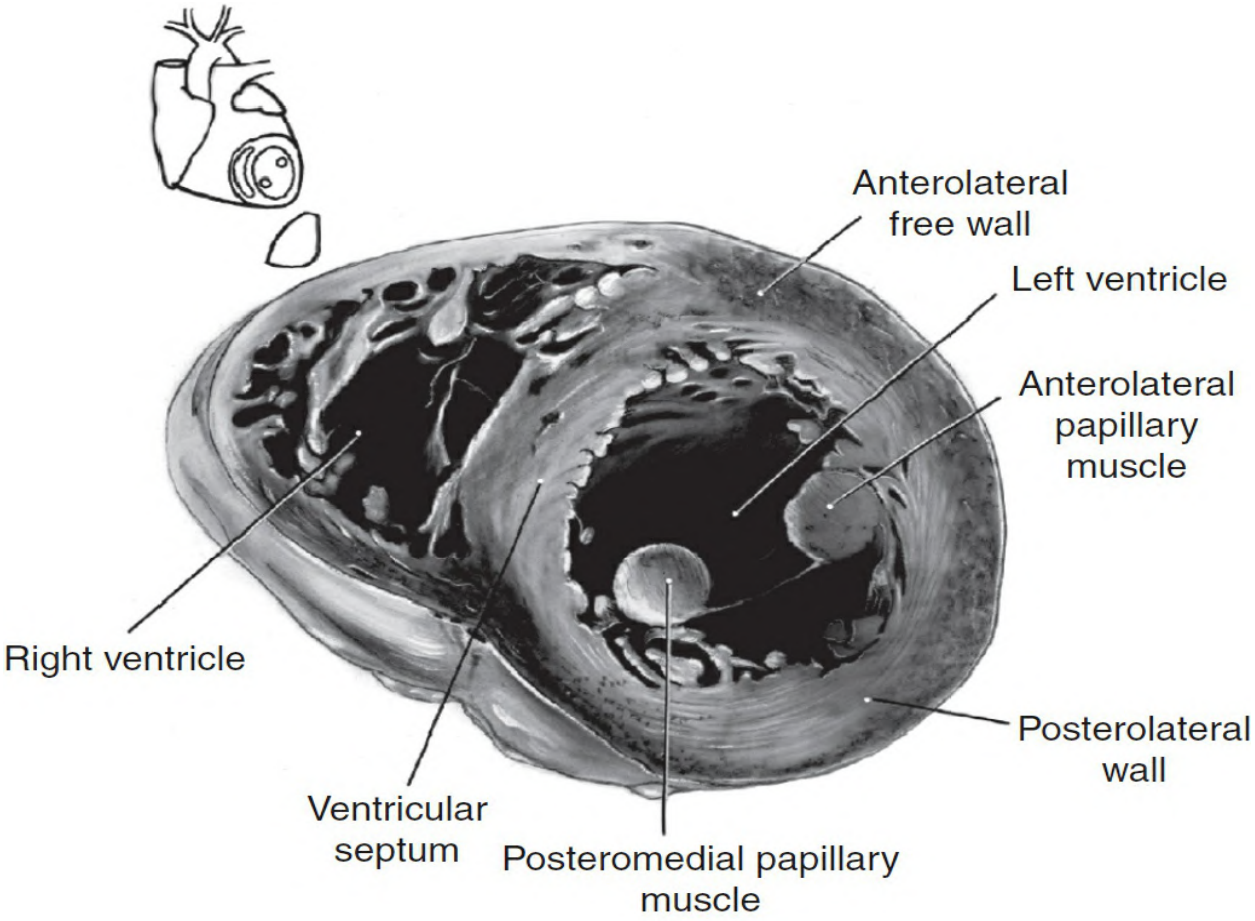

RV
VS
Ao
*
LV
LA
PW

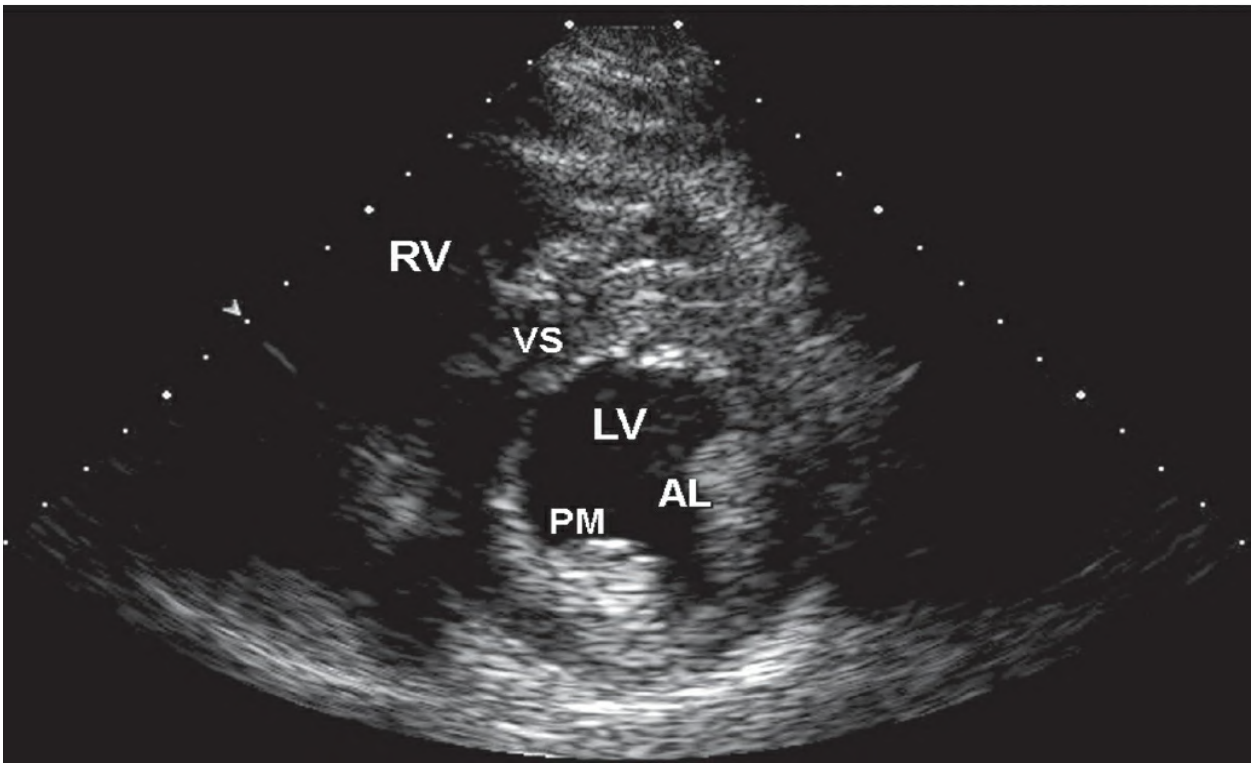
1 Parasternal long-axis view allows visualization of the right ventricle (RV), ventricular septum (VS), posterior wall (PW) aortic valve cusps, left ventricle (LV), mitral valve, left atrium (LA), and ascending thoracic aorta (Ao). *Pulmonary artery. (Top: Redrawn from *Mayo Clin Proc* 1978;53(5):271–303. Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved. Bottom: From *The Echo Manual*, 3rd ed, 2006:10. Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved.)


Anterior tricuspid leaflet
Right ventricular outflow tract
Right coronary cusp
Pulmonary valve
Right coronary artery
Left coronary artery
Left atrial appendage
Right atrium
Left coronary cusp
Noncoronary cusp
Left atrium
Inferior vena cava
Atrial septum
Coronary sinus

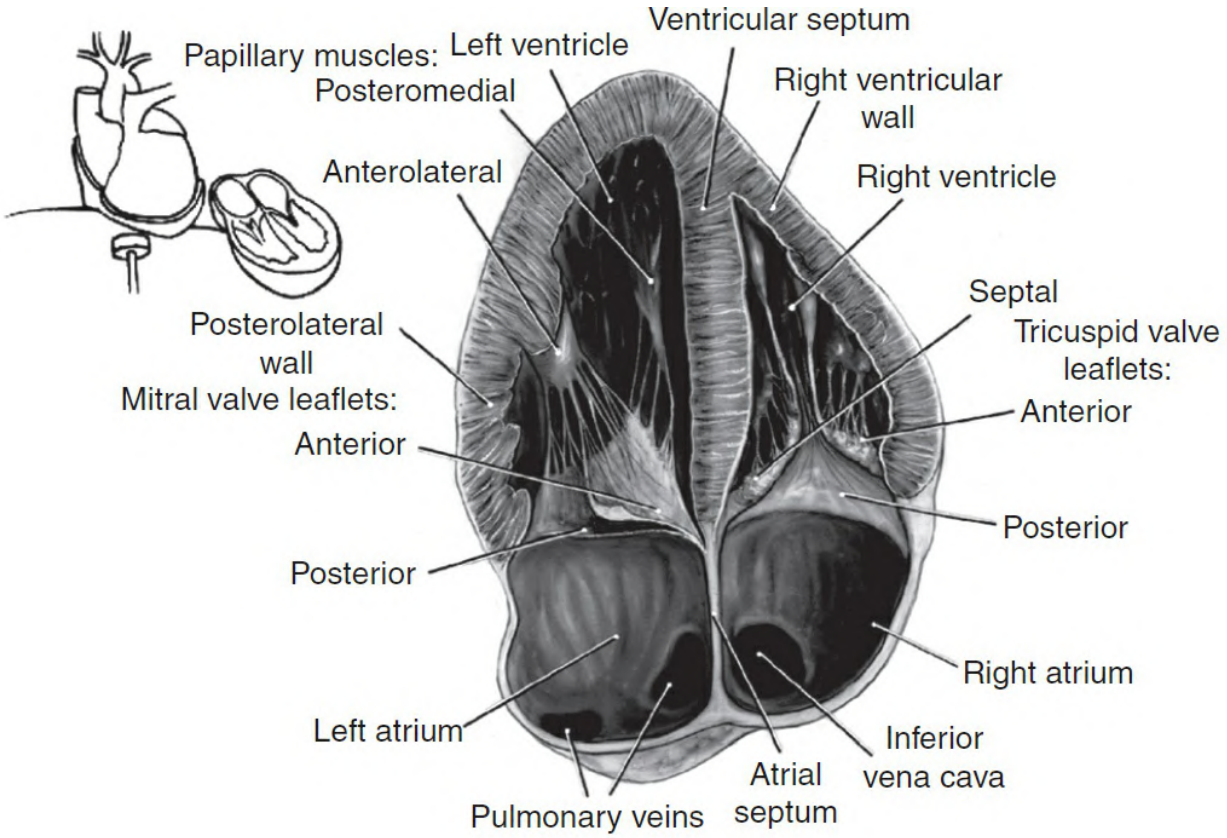

RVOT
PV
RA
LA

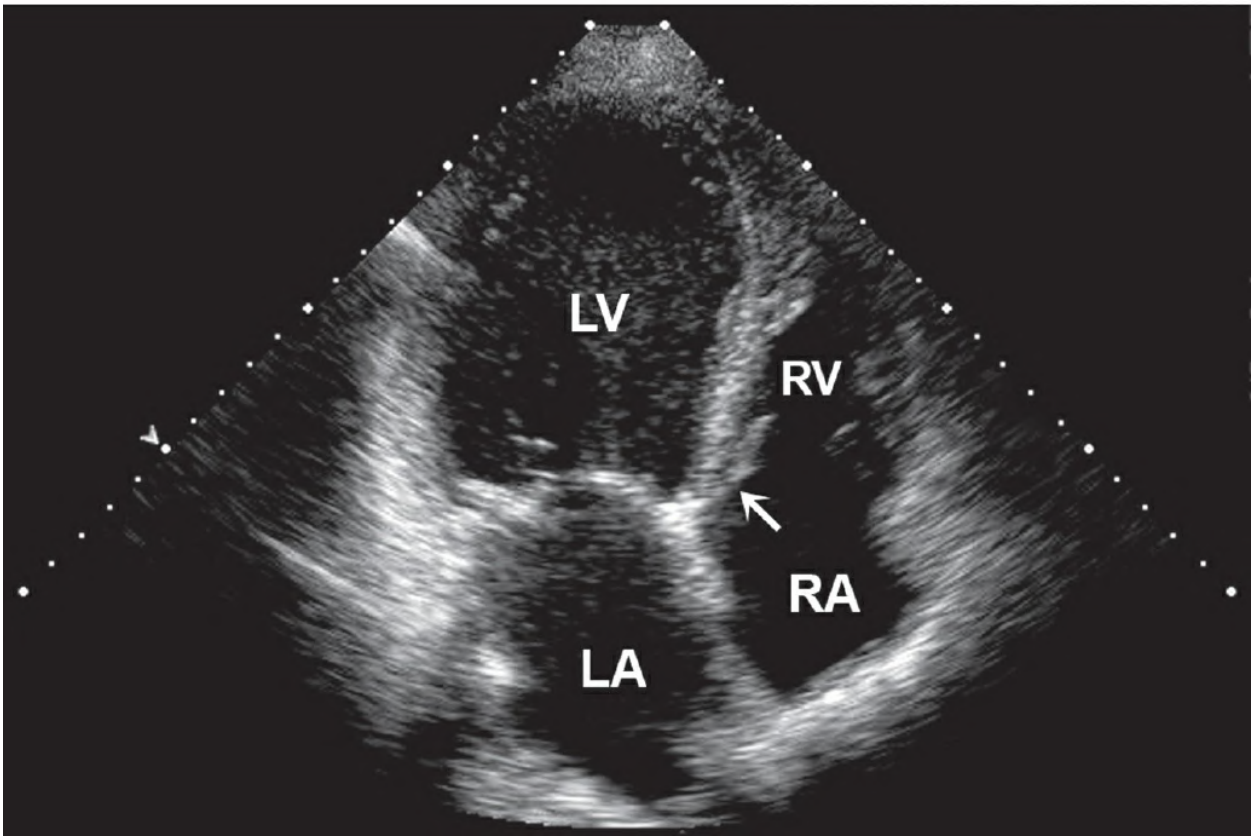
2 Parasternal short-axis view at the level of the aorta: LA, left atrium; PV, pulmonary valve; RA, right atrium; RVOT, right ventricular outflow tract. (Top: Redrawn from *Mayo Clin Proc* 1978;53(5):271–303. Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved. Bottom: From *The Echo Manual*, 3rd ed, 2006:13. Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved.)


Anterolateral free wall
Left ventricle
Anterolateral papillary muscle
Right ventricle
Posterolateral wall
Ventricular septum
Posteromedial papillary muscle


RV
VS
LV
AL
PM

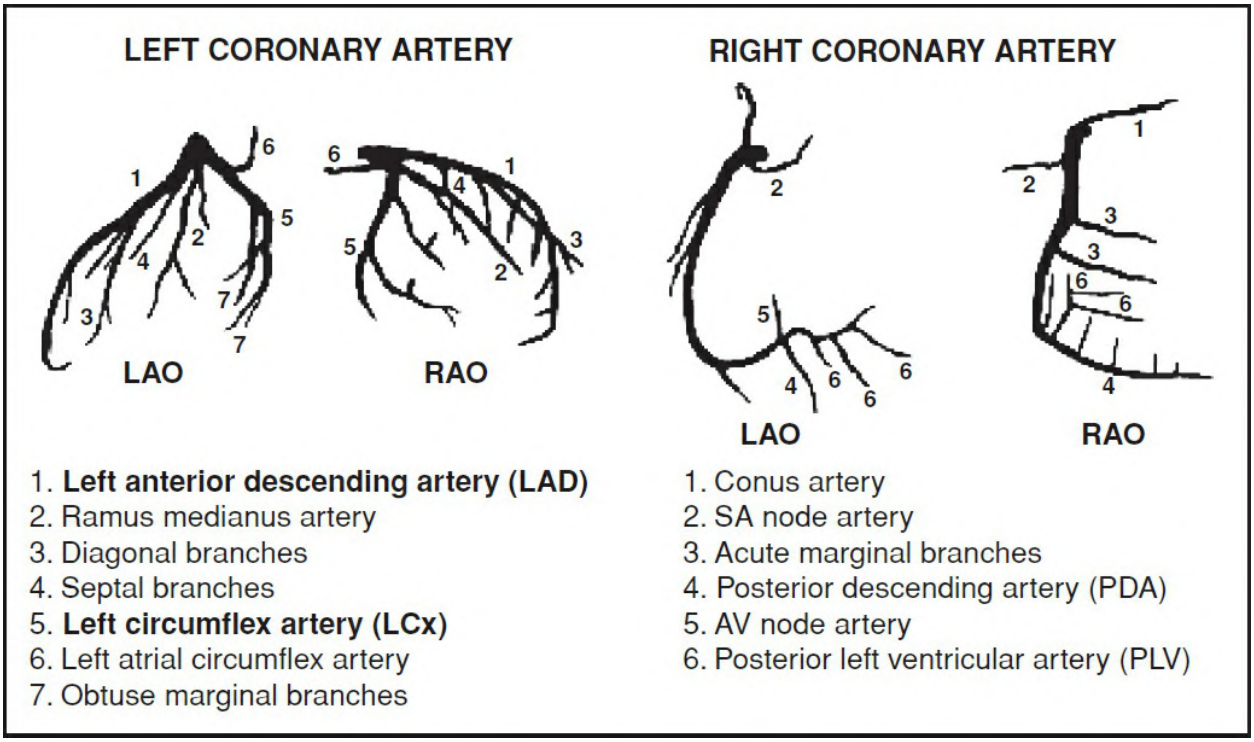
3 Parasternal short-axis view at the level of the papillary muscles: AL, anterolateral papillary muscle; LV, left ventricle; PM, posteromedial papillary muscle; RV, right ventricle; VS, ventricular septum. (Top: Redrawn from *Mayo Clin Proc* 1978;53(5):271–303. Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved. Bottom: From *The Echo Manual*. 3rd ed, 2006:12. Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved.)


Papillary muscles:
Posteromedial
Left ventricle
Ventricular septum
Right ventricular wall
Anterolateral
Right ventricle
Septal
Tricuspid valve leaflets:
Anterior
Posterolateral wall
Mitral valve leaflets:
Anterior
Posterior
Posterior
Right atrium
Left atrium
Inferior vena cava
Atrial septum
Pulmonary veins


LV
RV
RA
LA

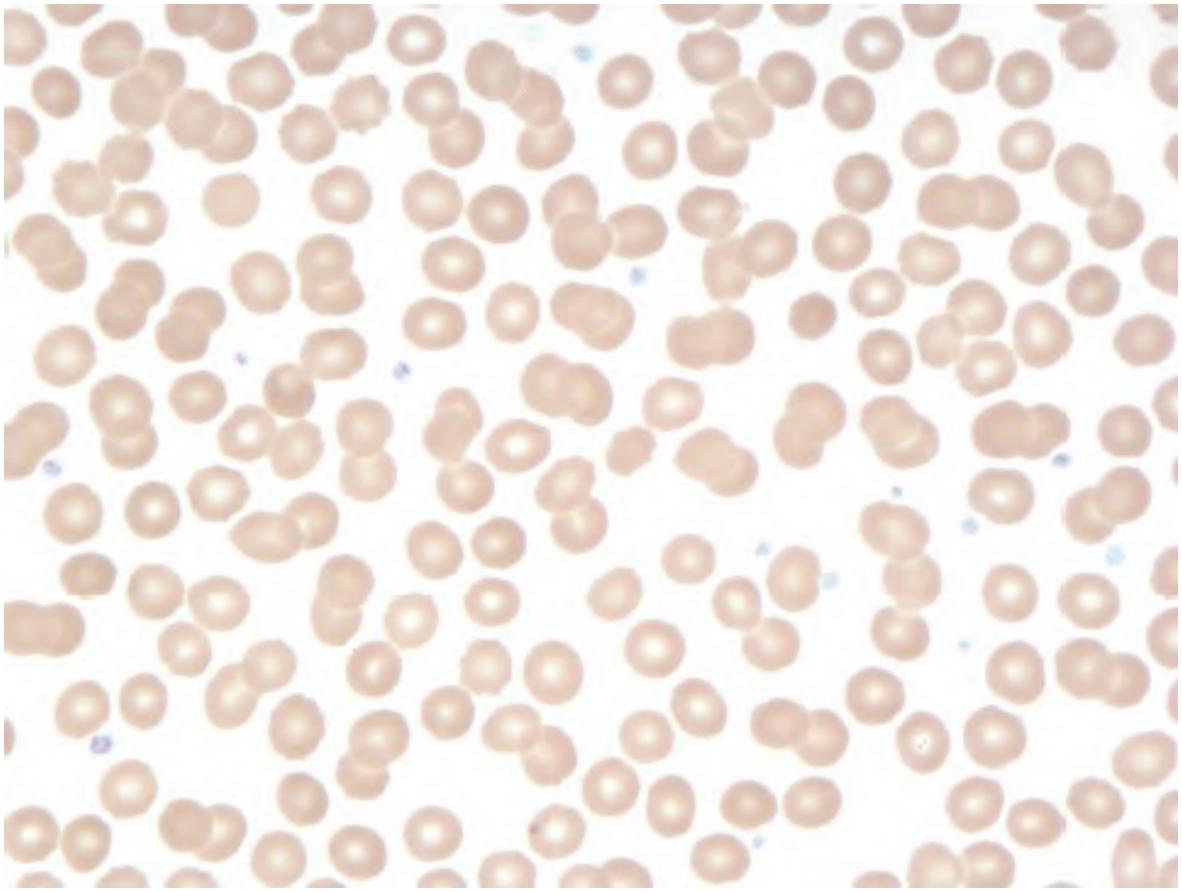
4 Apical four-chamber view: Note that at some institutions the image is re- versed so that the left side of the heart appears on the right side of the screen. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (Top: Redrawn from *Mayo Clin Proc* 1978;53(5):271–303. Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved. Bottom: From *The Echo Manual*, 3rd ed, 2006:14. Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

Coronary Angiography

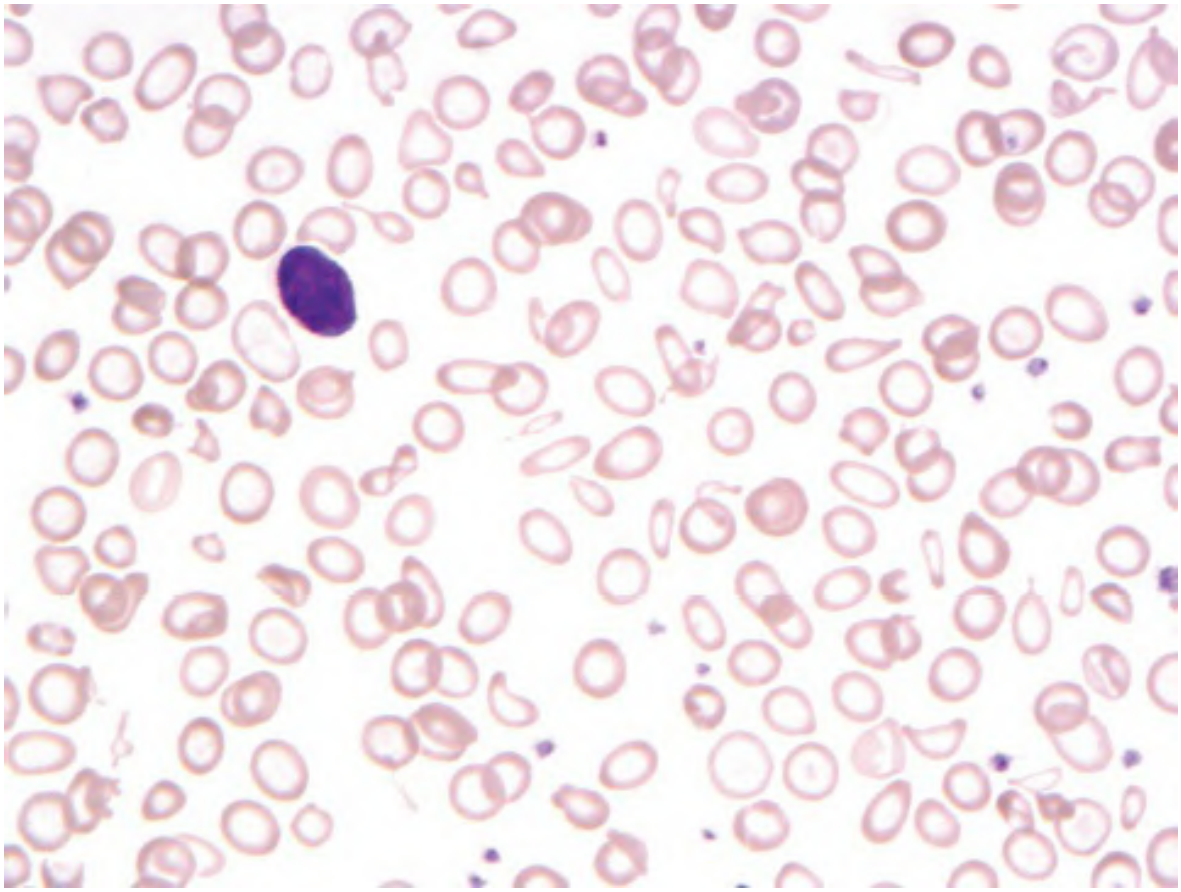


Coronary arteries. (Reprinted with permission from *Cardiac Catheterization, Angiography, and Intervention*, 4th ed, 1991.)

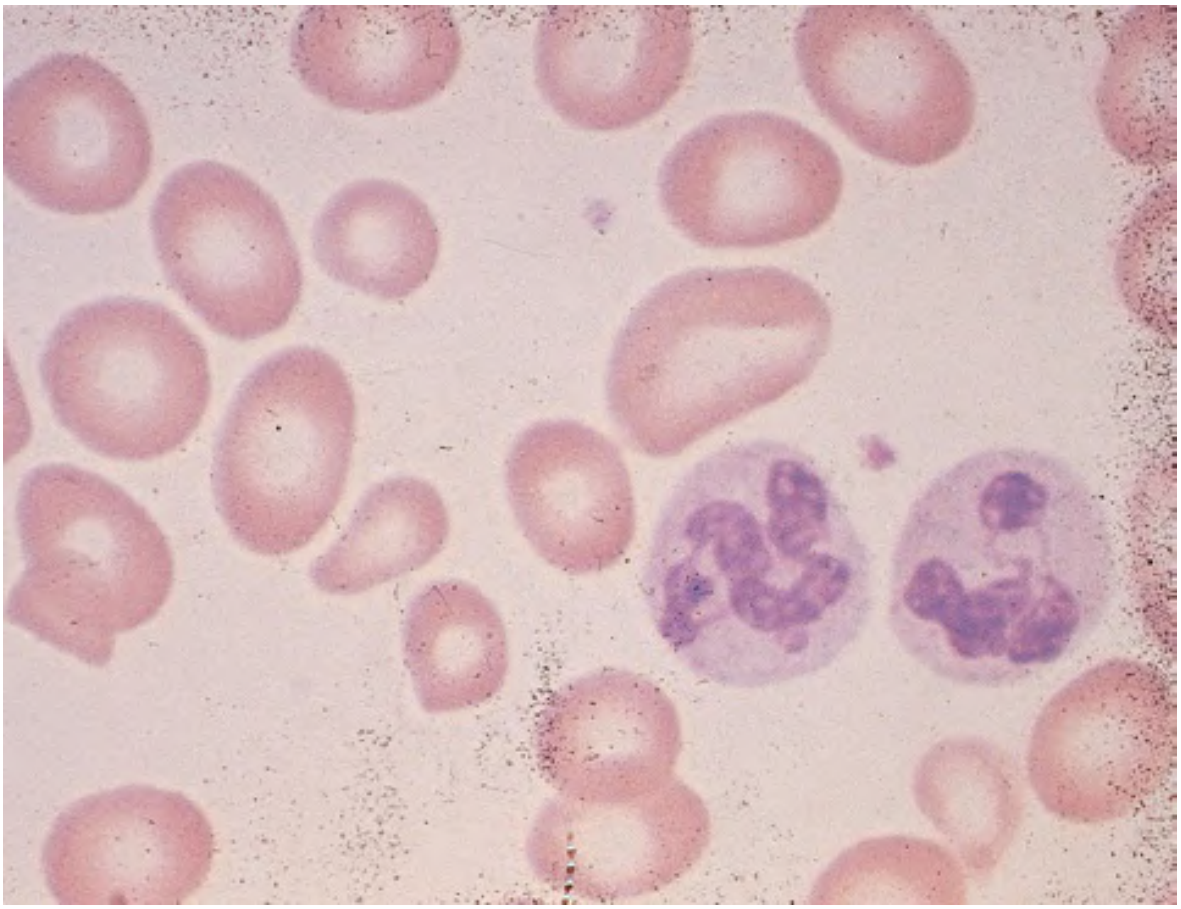
Peripheral Blood Smears



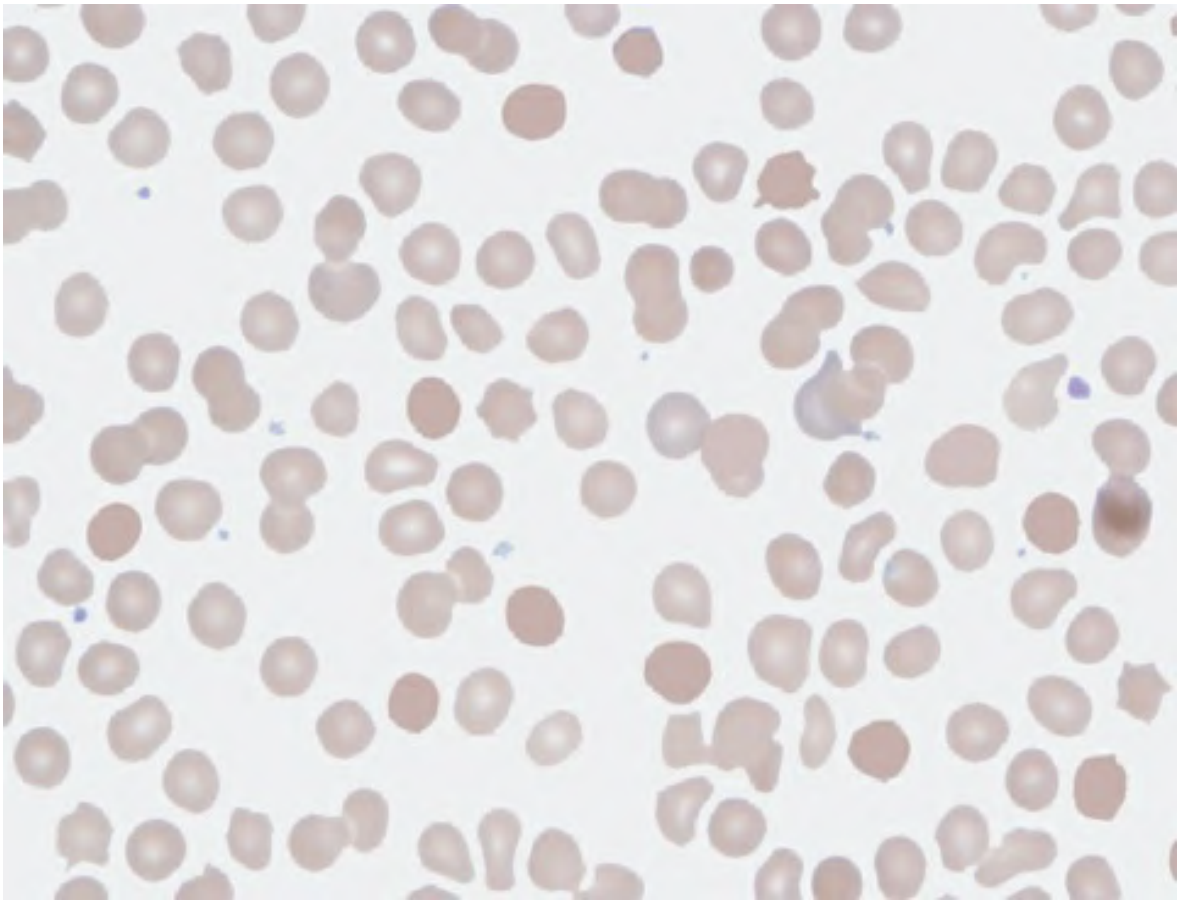
1 Normal smear.



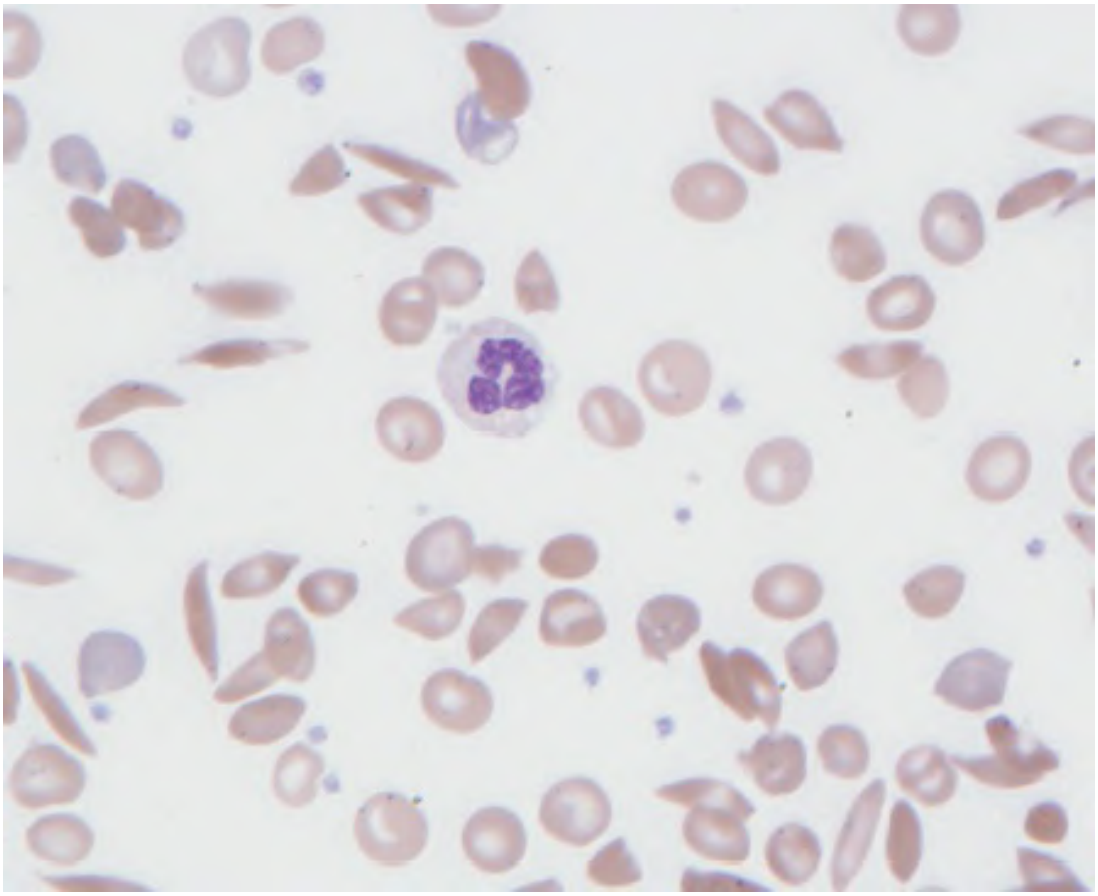
2 Hypochromic, microcytic anemia due to iron-deficiency.



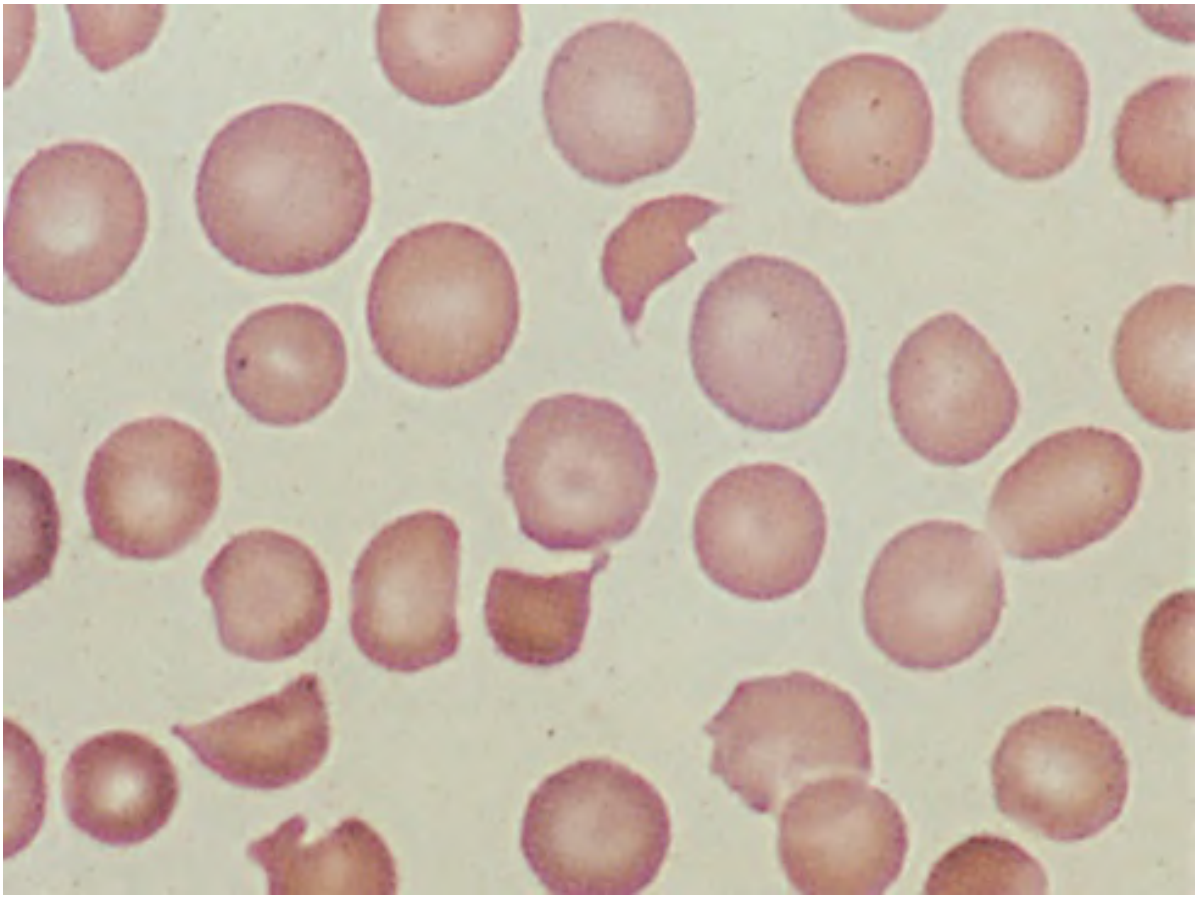
3 Macrocytic anemia due to pernicious anemia; note macro-ovalocytes and hypersegmented neutrophils.



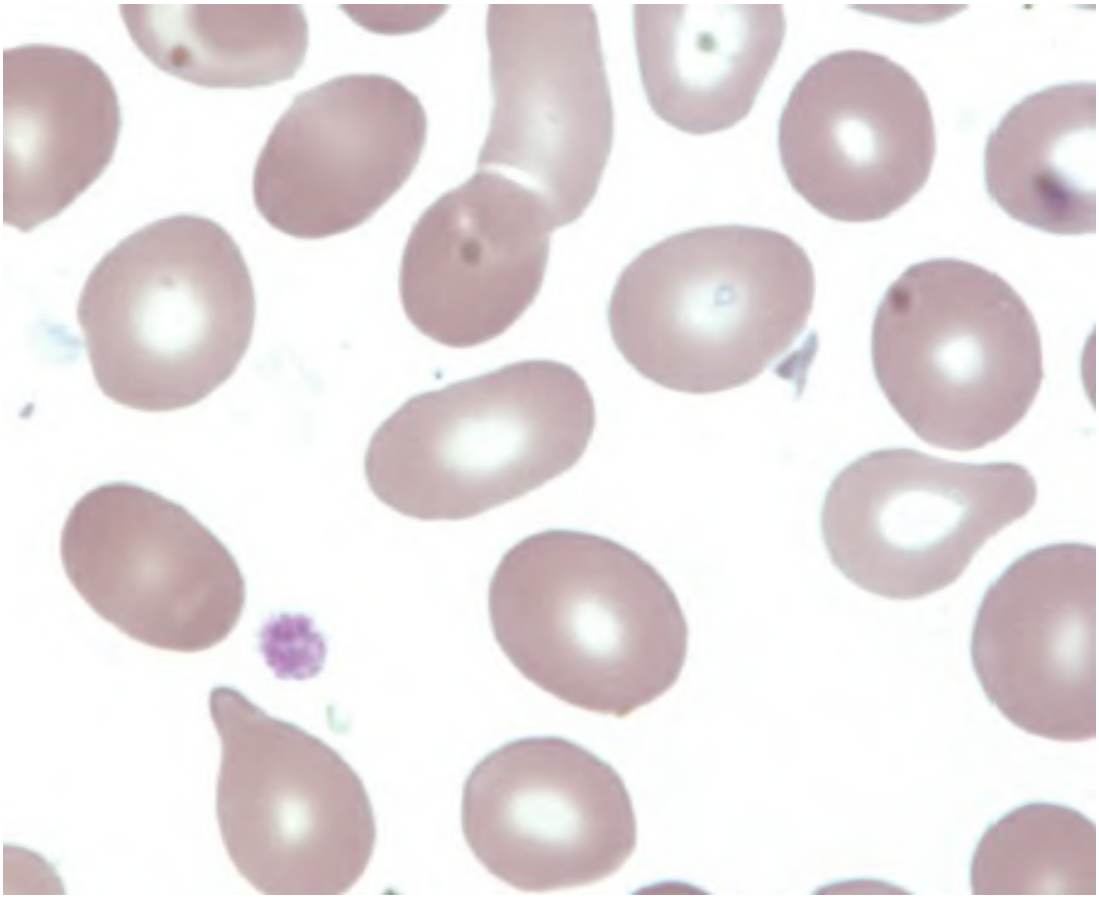
4 Spherocytes due to autoimmune hemolytic anemia.



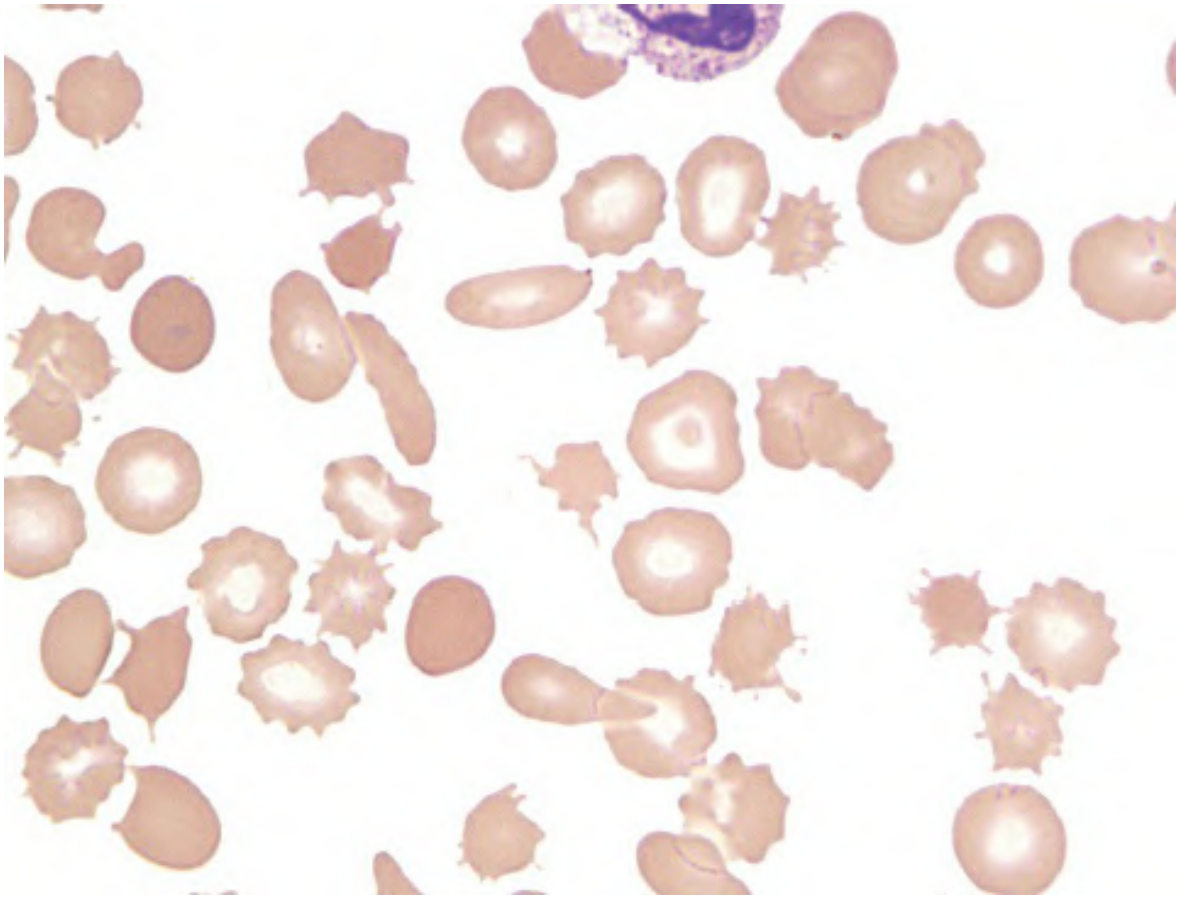
5 Sickle cell anemia.



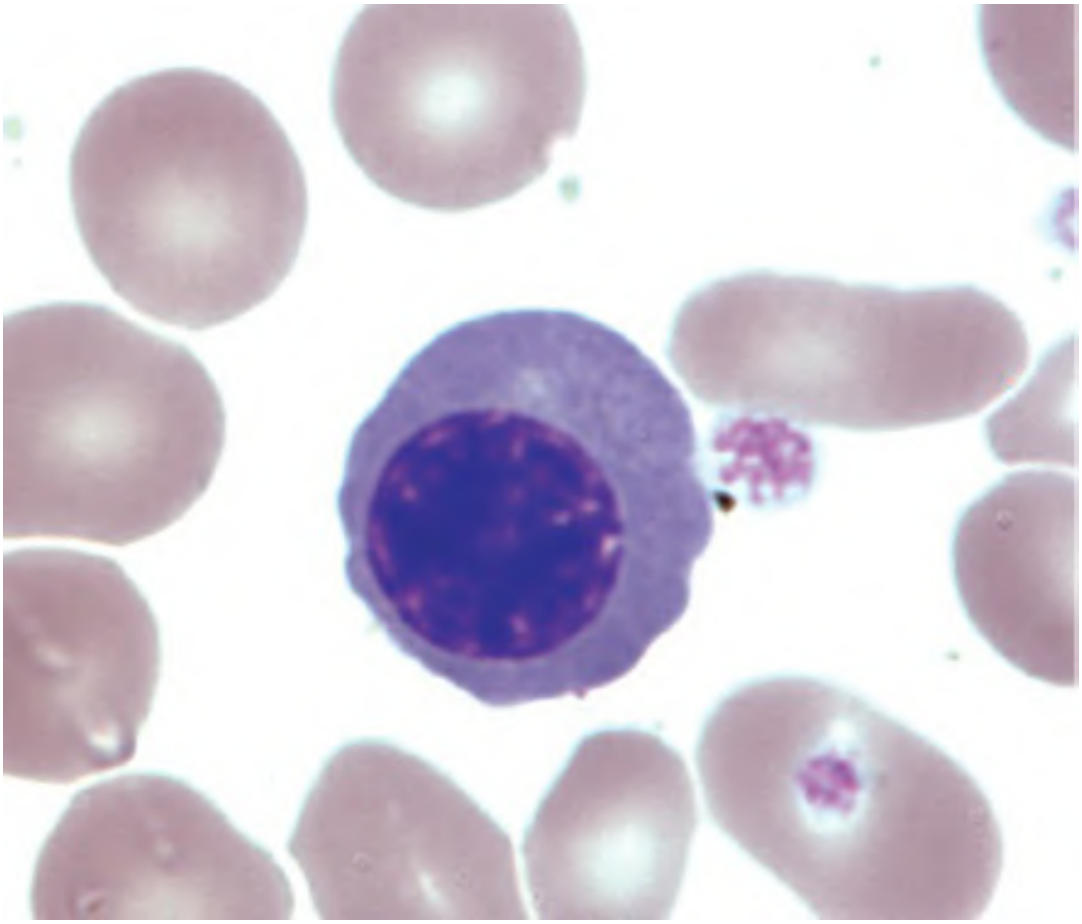
6 Schistocytes.



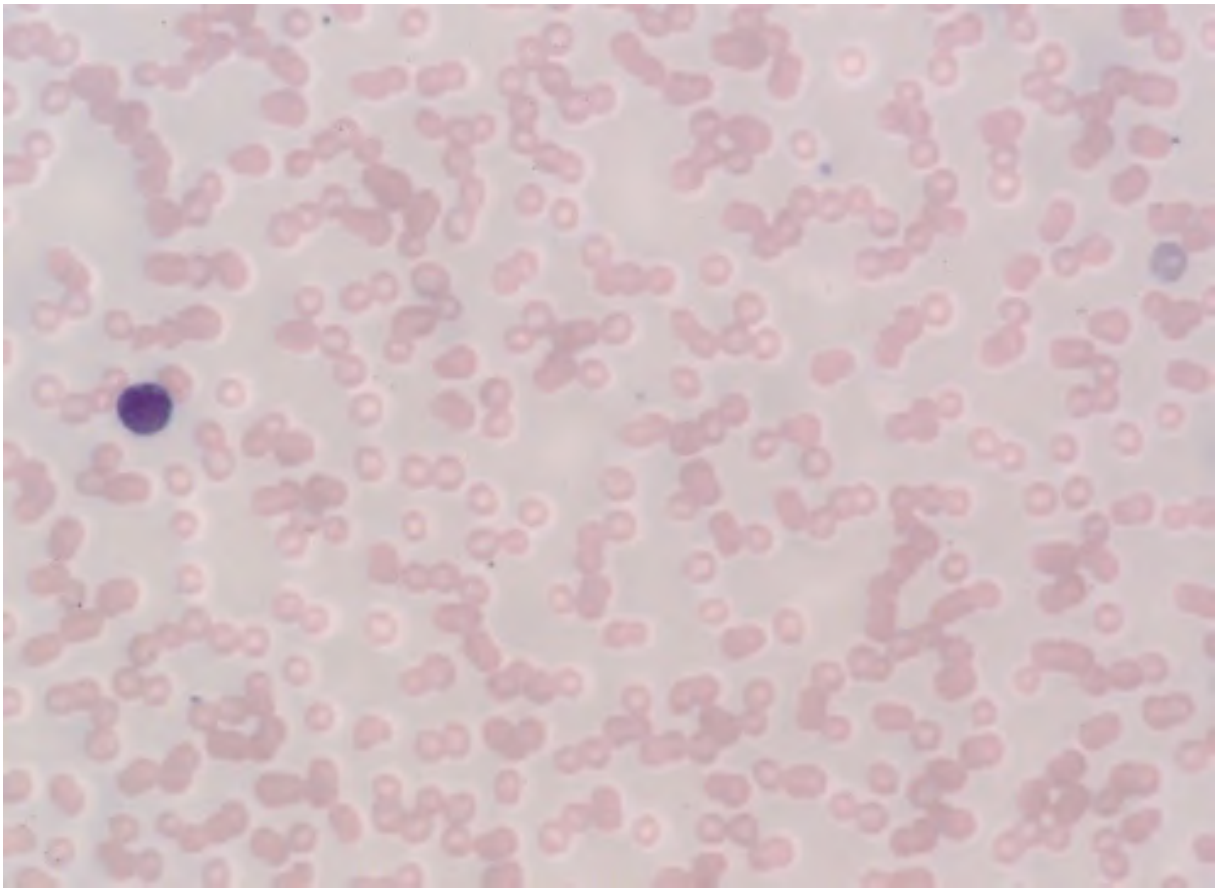
7 Teardrop shaped RBC (dacrocyte).



8 Acanthocytes.

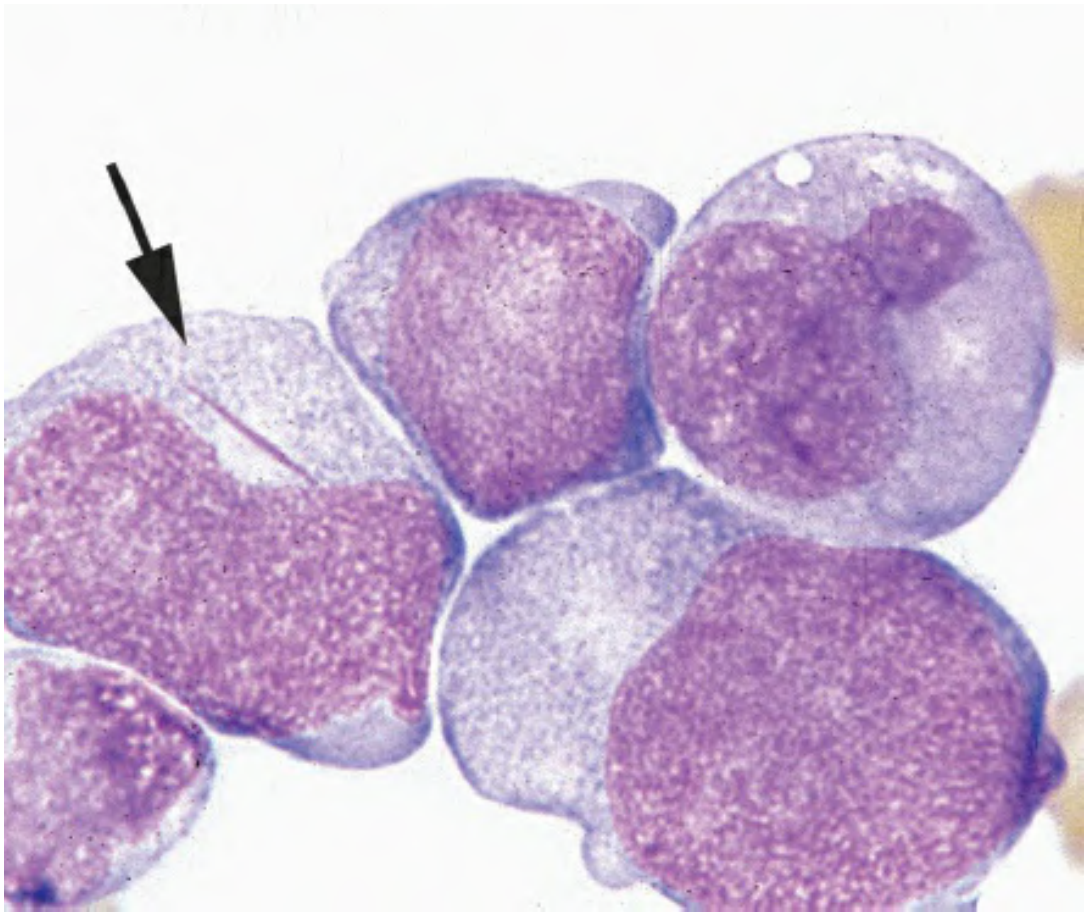


9 Nucleated RBC.

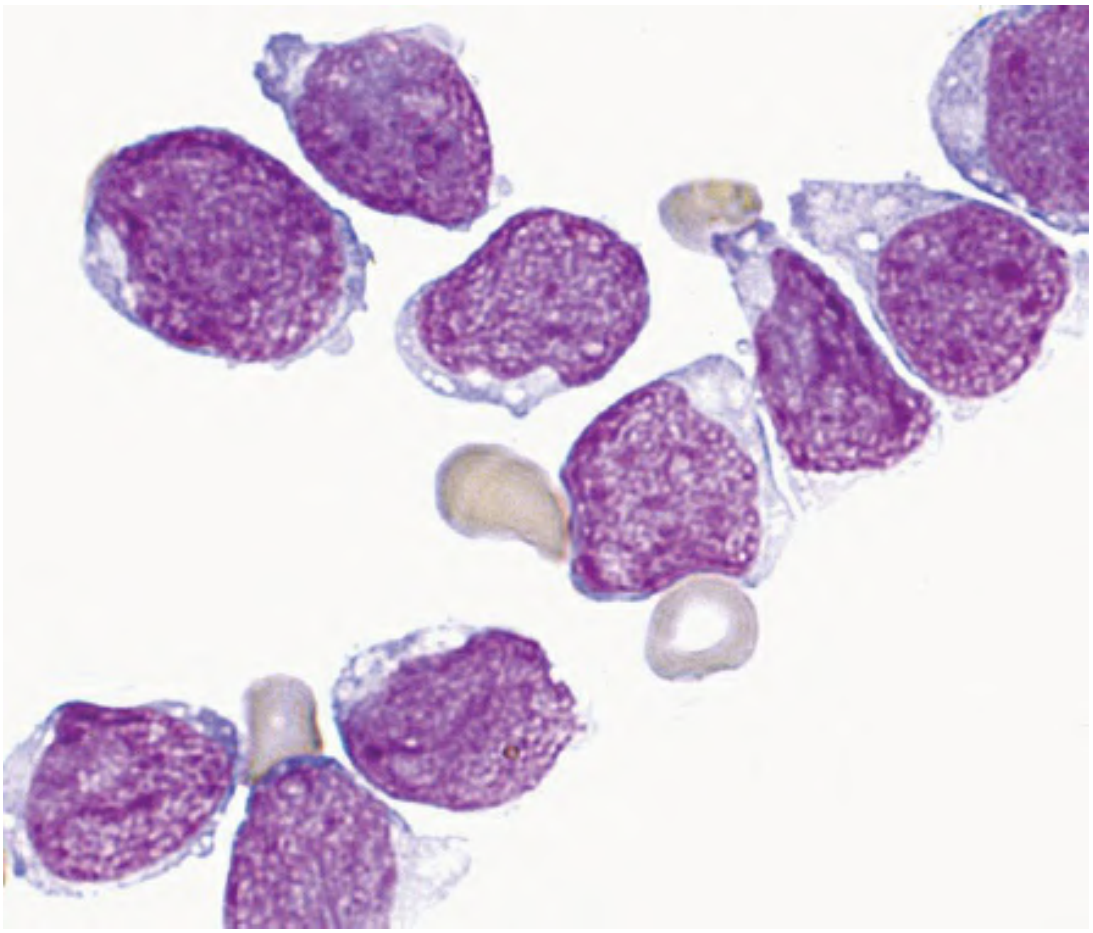


10 Rouleaux.

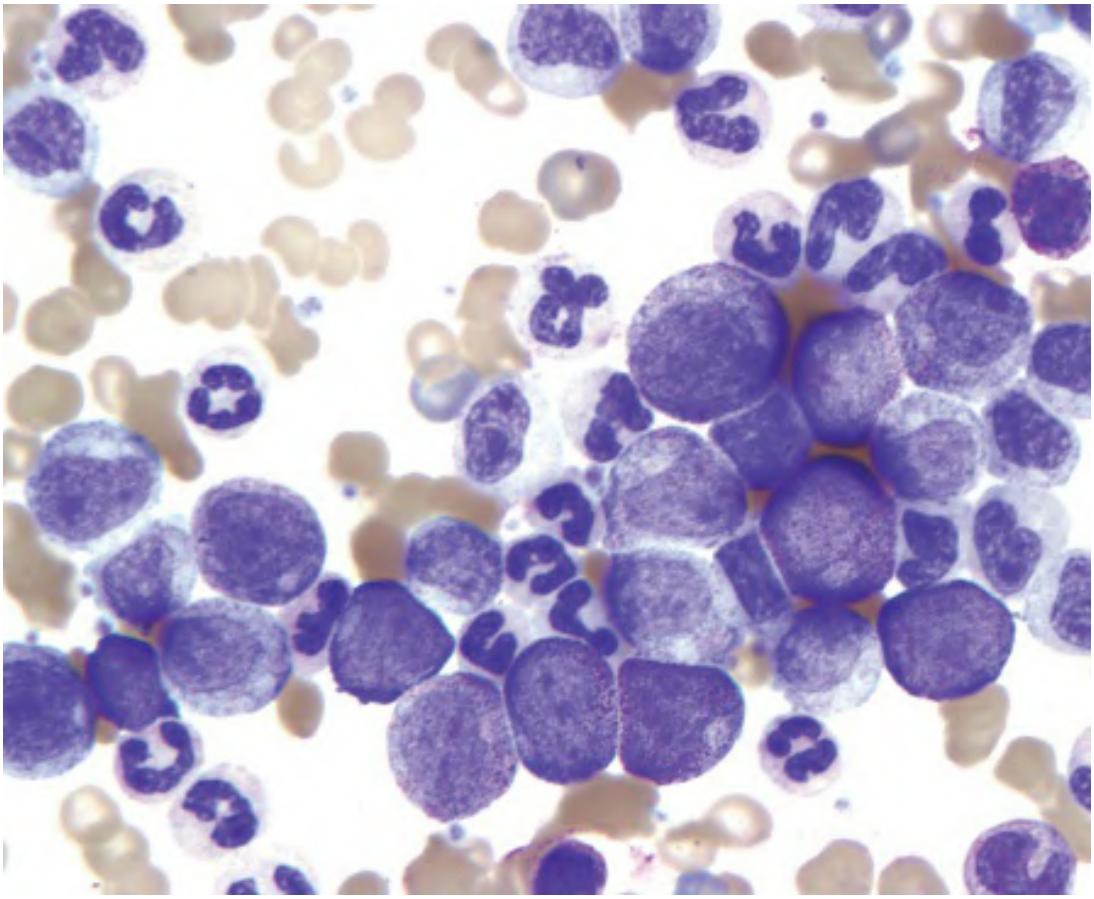
Leukemias



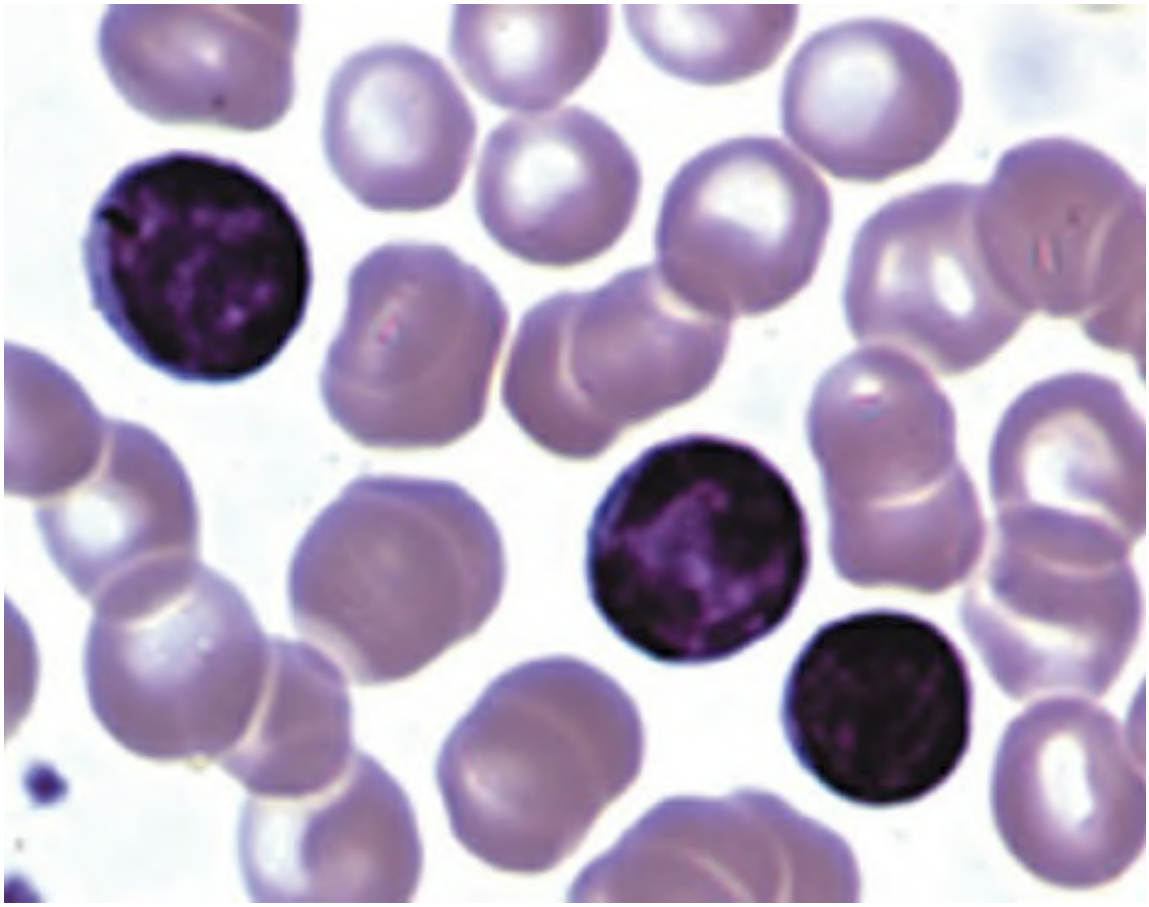
1 AML with Auer rod.



2 ALL.



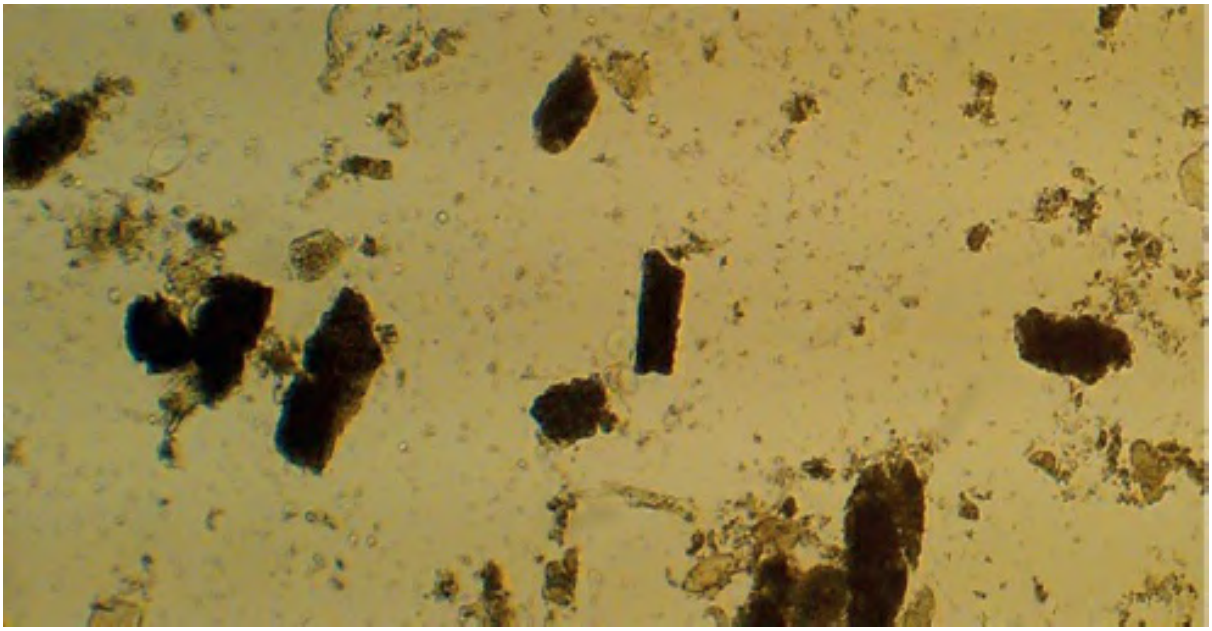
3 CML.



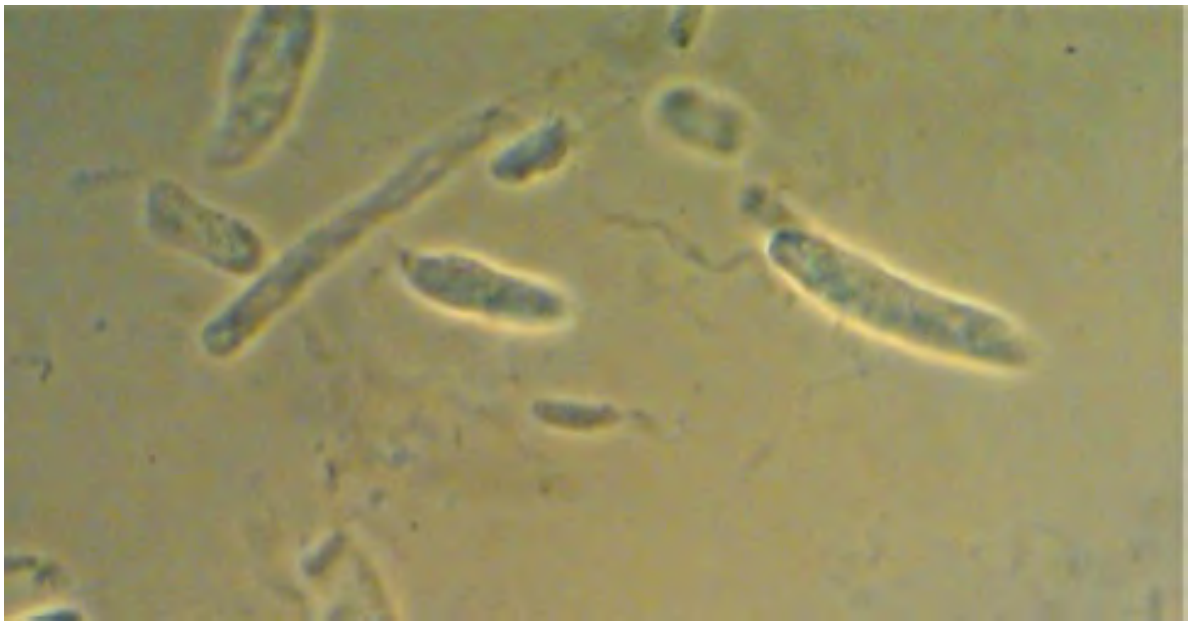
4 CLL.

All photos excluding Leukemias Fig. 4 reprinted with permission from *Wintrobe's Clinical Hematology,* 12th ed, 2009. Leukemias Fig. 4 reprinted with permission from *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology*, 8th ed, 2008.

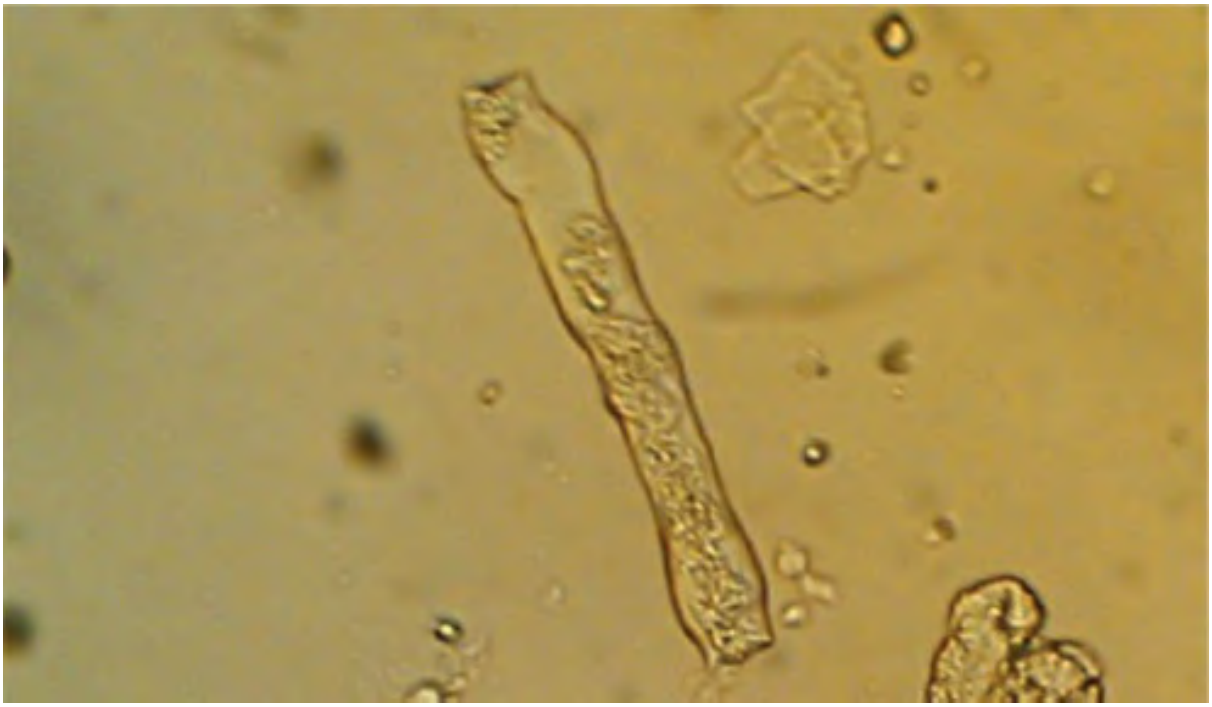
Urinalysis



1 “Muddy brown” or granular cast (Courtesy of Nicholas Zwang, MD.)

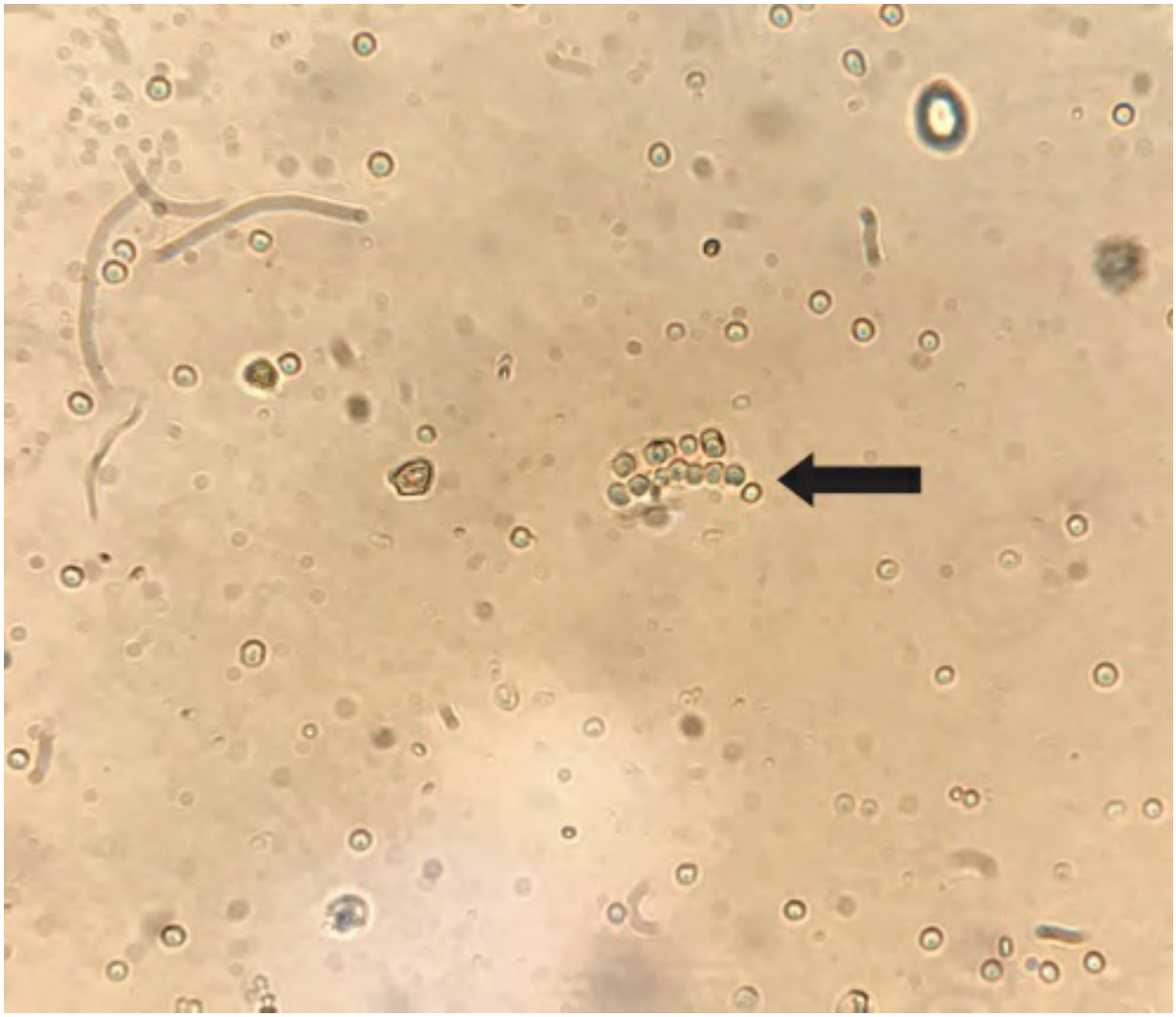


2 Hyaline cast (Courtesy of Nicholas Zwang, MD.)

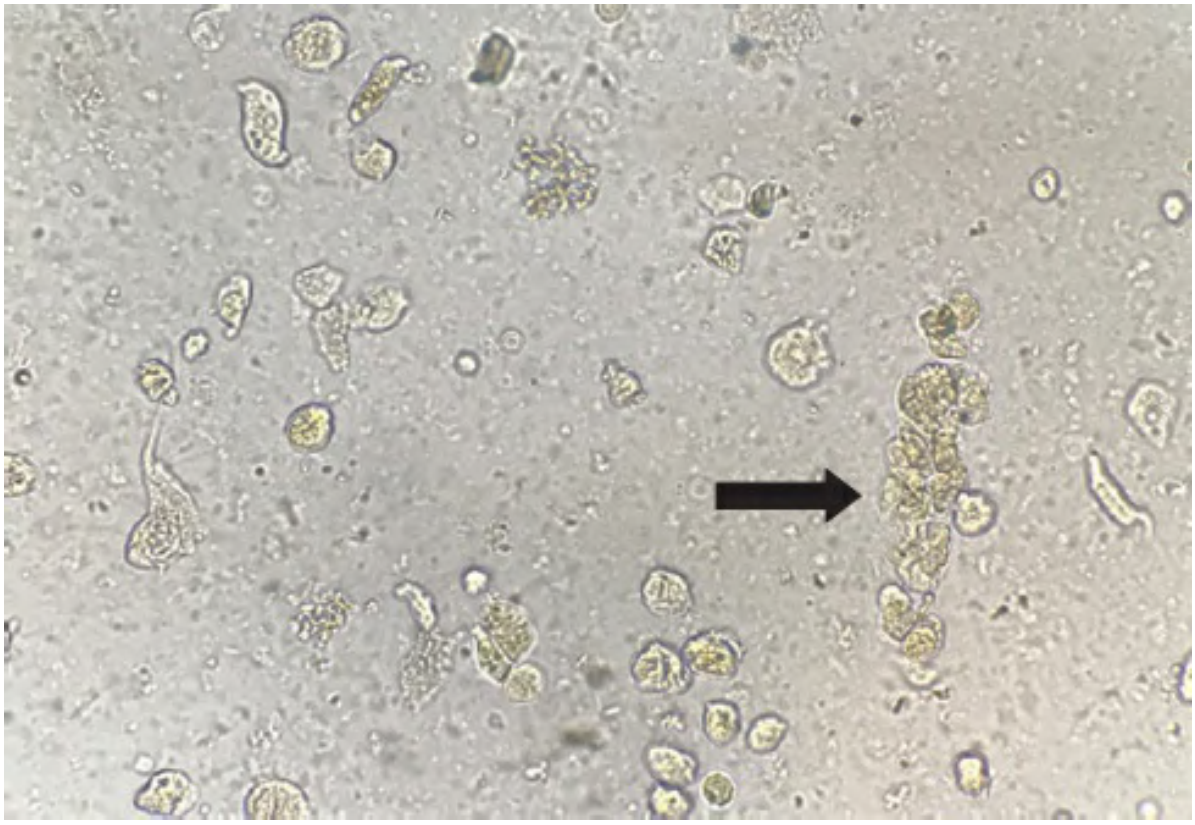


3 “Waxy broad” cast (Courtesy of Nicholas Zwang, MD.)

4 Renal tubular epithelial cell (Courtesy of Nicholas Zwang, MD.)

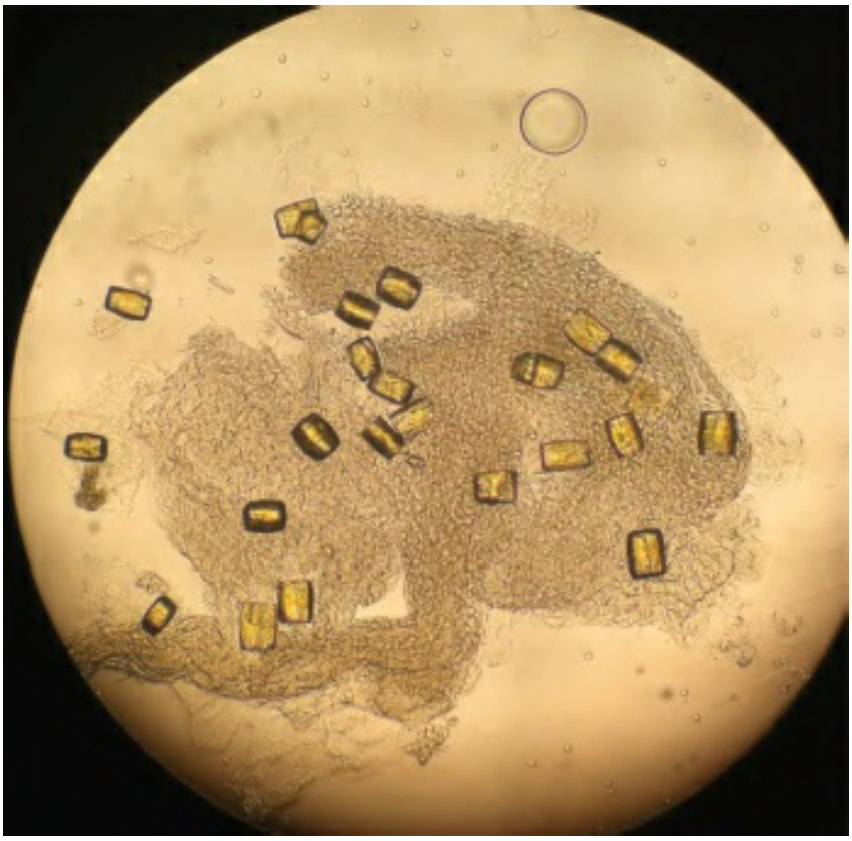


5 RBC cast (Courtesy of Harish Seethapathy, MBBS.)

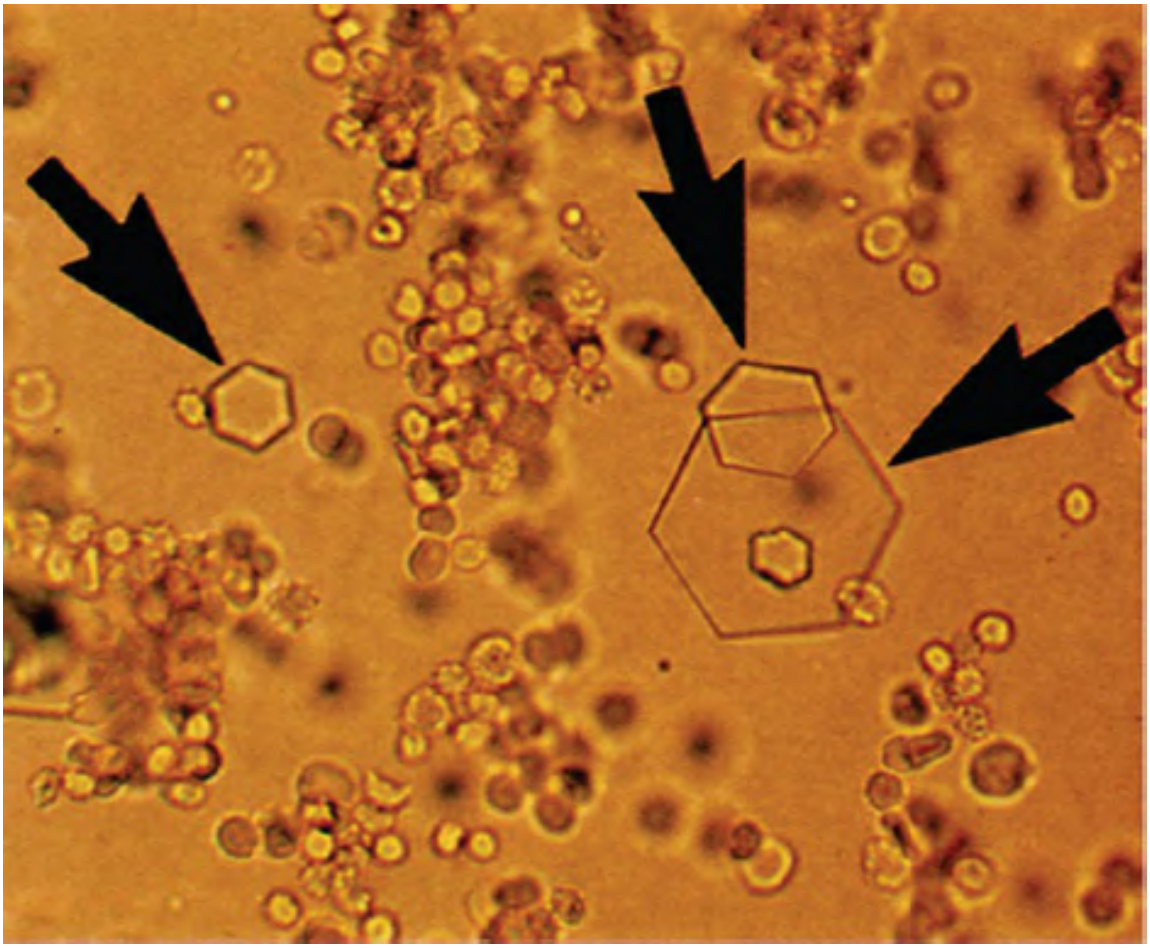


6 WBC cast (Courtesy of Harish Seethapathy, MBBS.)

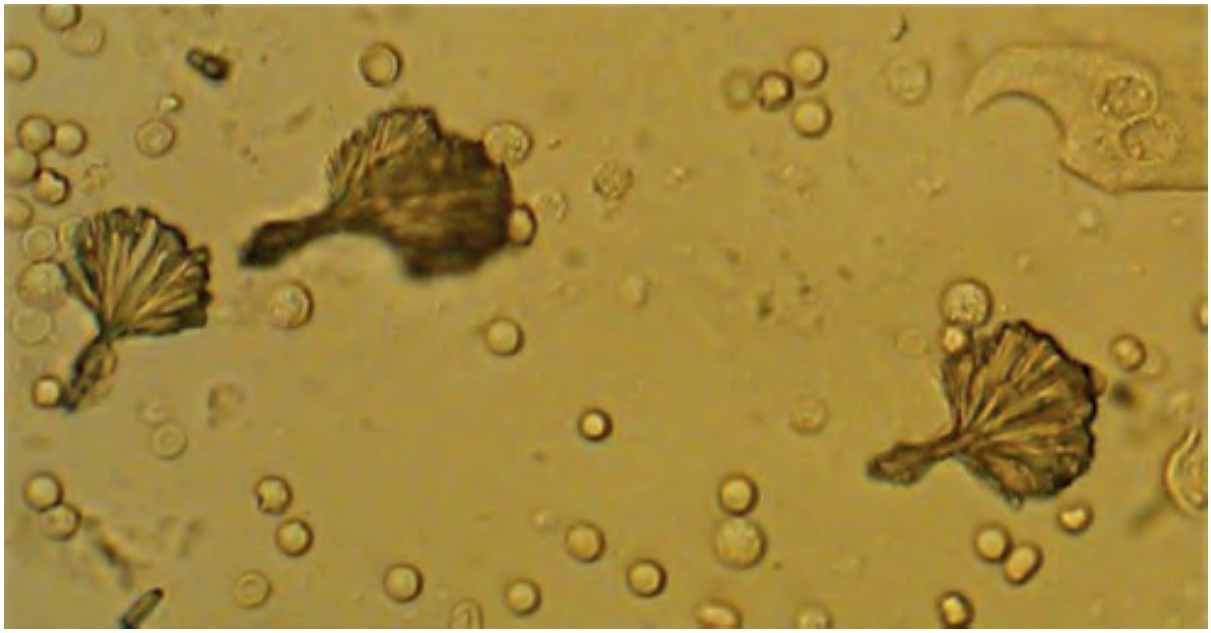
7 Calcium oxalate crystals (Courtesy of Mallika Mendu, MD.). Calcium dihydrate (arrow), calcium monohydrate (dashed arrow), and amorphous calcium crystals (arrow-head)



8 “Struvite” magnesium ammonia phosphate crystals (Courtesy of Brett Carroll, MD.)

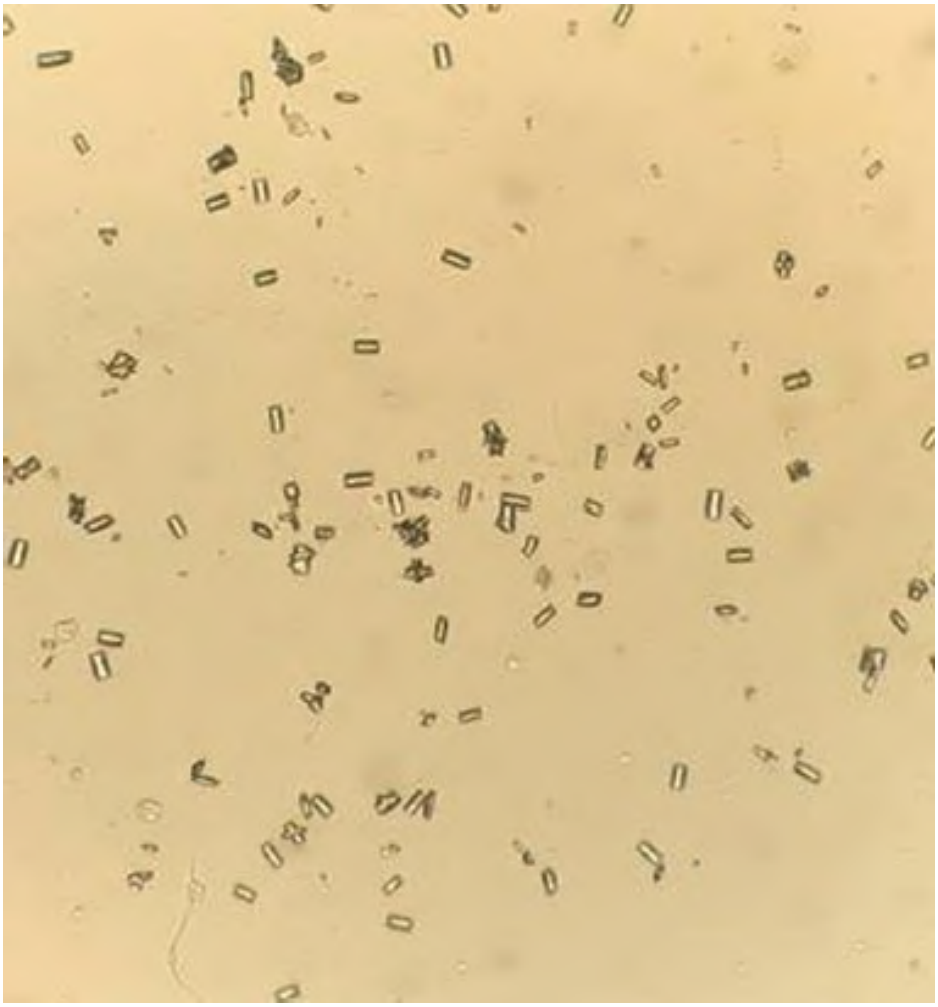


9 Cystine crystals (Reprinted with permission from *Clinical Laboratory Medicine,* 1994.)

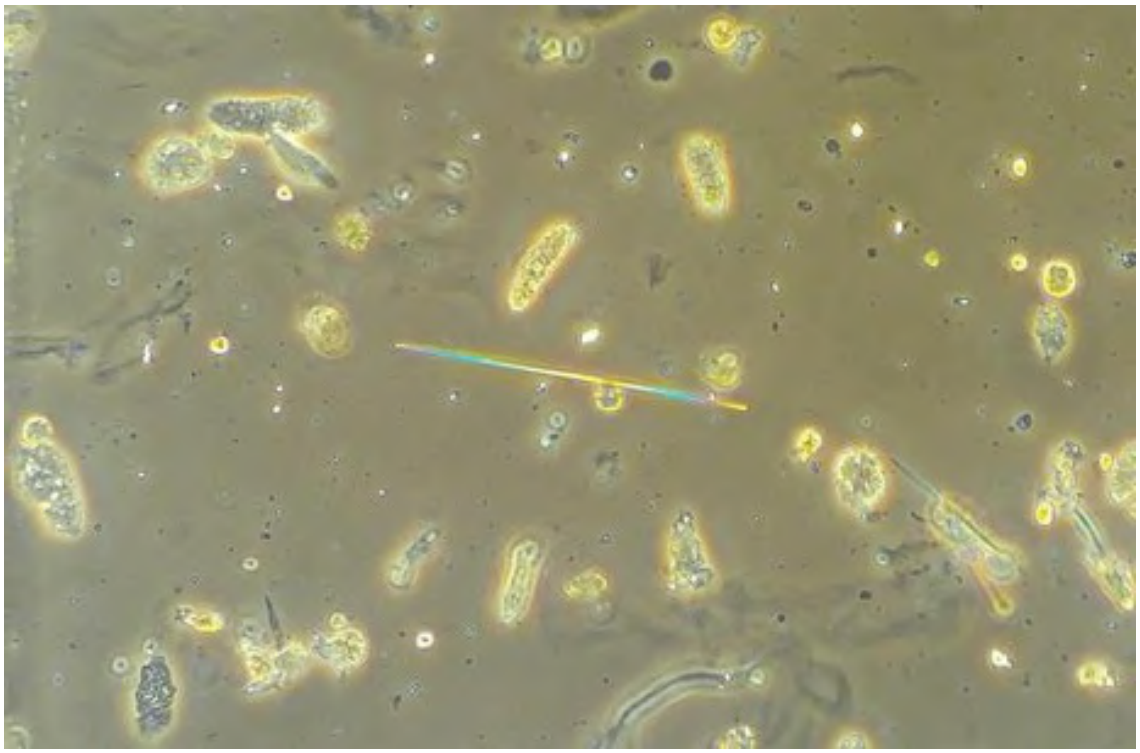


10 Sulfadiazine “shock of wheat” crystals (Courtesy of Nicholas Zwang, MD.)

11a Uric acid crystals under polarized light (Courtesy of Harish Seethapathy, MBBS.)



11b Uric acid crystals under normal light (Courtesy of Harish Seethapathy, MBBS.)



12 Acyclovir needle crystals (Courtesy of Yuvaram Reddy, MBBS.)

ABBREVIATIONS

5′-NT 5′-nucleotidase

6-MP 6-mercaptopurine

a/c anticoagulation

a/w associated with

AAA abdominal aortic aneurysm

AAD antiarrhythmic drug

Ab antibody

ABE acute bacterial endocarditis

ABG arterial blood gas

abnl abnormal

ABPA allergic bronchopulm. aspergillosis

abx antibiotics

AC assist control

ACE angiotensin-converting enzyme

ACEI ACE inhibitor

ACI anemia of chronic inflammation

ACL anticardiolipin antibody

ACLS advanced cardiac life support

ACM arrhythmogenic RV CMP

ACS acute coronary syndrome

ACTH adrenocorticotropic hormone

ACV acyclovir

ADA adenosine deaminase

ADH antidiuretic hormone

ADLs activities of daily living

AF atrial fibrillation

AFB acid-fast bacilli

AFL atrial flutter

AFP α-fetoprotein

AFTP ascites fluid total protein

AG aminoglycoside anion gap

Ag antigen

AGN acute glomerulonephritis

AI adrenal insufficiency aortic insufficiency aromatase inhibitor
AIDS acquired immunodefic. synd.
AIH autoimmune hepatitis
AIHA autoimmune hemolytic anemia
AIN acute interstitial nephritis
AIP acute interstitial pneumonia
AKI acute kidney injury
ALF acute liver failure
ALL acute lymphoblastic leukemia
ALS amyotrophic lateral sclerosis
ALT alanine aminotransferase
AMA anti-mitochondrial antibody
AMI anterior myocardial infarction
AML acute myelogenous leukemia
amy amylase
ANA antinuclear antibody
ANCA antineutrophilic cytoplasmic Ab
AoD aortic dissection
AoV aortic valve
APAP acetyl-para-aminophenol
APC activated protein C
APL acute promyelocytic leukemia
APLA antiphospholipid Ab
APS antiphospholipid Ab synd.
ARB angiotensin receptor blocker
ARDS acute resp. distress synd.
ARV antiretroviral
ARVC arrhythmogenic RV CMP
AS aortic stenosis
ASA aspirin
ASD atrial septal defect
AST aspartate aminotransferase
asx asymptomatic
AT atrial tachycardia
ATII angiotensin II
ATN acute tubular necrosis
ATRA all-trans-retinoic acid
AV atrioventricular
AVA aortic valve area

AVB atrioventricular block
AVNRT AV nodal reentrant tachycardia
AVR aortic valve replacement
AVRT AV reciprocating tachycardia
AZA azathioprine
Aφ alkaline phosphatase
b/c because
BAL bronchoalveolar lavage
BBB bundle branch block
BCx blood culture
BD bile duct
bili. bilirubin
BiPAP bilevel positive airway pressure
BiV biventricular
BM bone marrow bowel movement
BMD bone mineral density
BMI body mass index
BMS bare metal stent
BNP B-type natriuretic peptide
BP blood pressure
BPH benign prostatic hypertrophy
BRBPR bright red blood per rectum
BUN blood urea nitrogen
bx biopsy
BCYE buffered charcoal yeast extract
BZD benzodiazepines
βB beta-blocker
c/f concern for
c/s consult
c/w compared with consistent with
C′ complement
CABG coronary artery bypass grafting
CAD coronary artery disease
CAH congenital adrenal hyperplasia
CAPD chronic amb. peritoneal dialysis
CBC complete blood count
CBD common bile duct
CCB calcium channel blocker

CCP cyclic citrullinated peptide
CCS Canadian Cardiovascular Society
CCTA coronary CT angiography
CCY cholecystectomy
CD Crohn's disease
CEA carcinoembryonic antigen carotid endarterectomy
ceph. cephalosporin
CF cystic fibrosis
CFU colony-forming units
CHB complete heart block
CHD congenital heart disease
CHF congestive heart failure
CI cardiac index
CIAKI contrast-induced AKI
CIDP chronic inflammatory demyelinating polyneuropathy
CJD Creutzfeldt-Jakob disease
CK creatine kinase
CKD chronic kidney disease
CLL chronic lymphocytic leukemia
CMC carpometacarpal (joint)
CML chronic myelogenous leukemia
CMML chronic myelomonocytic leukemia
CMP cardiomyopathy
CMV cytomegalovirus
CN cranial nerve
CNI calcineurin inhibitor
CNS central nervous system coagulase-negative *Staphylococci*
CO carbon monoxide cardiac output
COP cryptogenic organizing PNA
COPD chronic obstructive pulm. dis.
COX cyclo-oxygenase
CP chest pain
CPAP continuous positive airway pressure
CPP cerebral perfusion pressure
CPPD calcium pyrophosphate dihydrate
Cr creatinine
CrAg cryptococcal antigen
CRC colorectal cancer
CrCl creatinine clearance

CRP C-reactive protein
CRT cardiac resynchronization therapy
CsA cyclosporine A
CSF cerebrospinal fluid
CSM carotid sinus massage
CT computed tomogram
CTA CT angiogram
CTD connective tissue disease
CTX ceftriaxone
CV cardiovascular
CVA cerebrovascular accident
CVD cerebrovascular disease collagen vascular disease
CVID common variable immunodefic.
CVP central venous pressure
CVVH continuous veno-venous hemofiltration
CW chest wall
cx culture
CXR chest radiograph
CYC cyclophosphamide
d day
D death
d/c discharge discontinue
DA dopamine
DAD diffuse alveolar damage
DAH diffuse alveolar hemorrhage
DAT direct antiglobulin test
DBP diastolic blood pressure
DCCV direct current cardioversion
DCIS ductal carcinoma in situ
DCM dilated cardiomyopathy
DCT distal collecting tubule
Ddx differential diagnosis
DES drug-eluting stent
DFA direct fluorescent Ag detect.
DI diabetes insipidus
DIC disseminated intravasc. coag.
diff. differential
DIP desquamative interstitial pneumonitis distal interphalangeal (joint)
DKA diabetic ketoacidosis

DLCO diffusion capacity of the lung
DLE drug-induced lupus
DM dermatomyositis diabetes mellitus
DMARD disease-modifying antirheumatic drug
DOE dyspnea on exertion
DRE digital rectal exam
DRESS drug reaction w/ eosinophilia & systemic symptoms
DSE dobutamine stress echo
DST dexamethasone suppression test
DTRs deep tendon reflexes
DU duodenal ulcer
DVT deep vein thrombosis
dx diagnosis
ΔMS change in mental status
e/o evidence of
EAD extreme axis deviation
EAV effective arterial volume
EBV Epstein-Barr virus
ECG electrocardiogram
ECMO extracorporeal membrane oxygenation
ED emergency department
EDP end-diastolic pressure
EDV end-diastolic volume
EEG electroencephalogram
EF ejection fraction
EGD esophagogastroduodenoscopy
EGFR epidermal growth factor receptor
EGPA eosinophilic granulomatosis with polyangiitis
EI entry inhibitor
EIA enzyme-linked immunoassay
ELISA enzyme-linked immunosorbent assay
EM electron microscopy
EMB ethambutol
ENaC epithelial Na channel
ENT ears, nose, & throat
EOM extraocular movement/muscles
EP electrophysiology
Epo erythropoietin
EPS electrophysiology study

ERCP endoscopic retrograde cholangiopancreatography
ERV expiratory reserve volume
ESA erythropoiesis-stimulating agents
ESBL extended spectrum β-lactamase
ESP end-systolic pressure
ESR erythrocyte sedimentation rate
ESRD end-stage renal disease
ESV end-systolic volume
ET endotracheal essential thrombocythemia
EtOH alcohol
ETT exercise tolerance test
EUS endoscopic ultrasound
EVAR endovascular aneurysm repair
f/up follow-up
FDP fibrin degradation product
FEV_1 forced expir. vol in 1 sec
FFP fresh frozen plasma
FHx family history
FI fusion inhibitor
FMD fibromuscular dysplasia
FMF familial Mediterranean fever
FNA fine-needle aspiration
FOB fecal occult blood
FOBT fecal occult blood testing
FQ fluoroquinolone
FRC functional residual capacity
FSGS focal segmental glomerulosclerosis
FSH follicle-stimulating hormone
FUO fever of unknown origin
FVC forced vital capacity
G6PD glc-6-phosphate dehydrogenase
GB gallbladder
GBM glomerular basement membrane
GBS Guillain-Barré syndrome
GCA giant cell arteritis
GCS Glasgow Coma Scale
G-CSF granulocyte colony-stim. factor
GE gastroesophageal

gen. generation
GERD gastroesophageal reflux disease
GFR glomerular filtration rate
GGT γ-glutamyl transpeptidase
GH growth hormone
GIB gastrointestinal bleed
GIST gastrointestinal stromal tumor
glc glucose
GMCSF granulocyte-macrophage colony-stimulating factor
GN glomerulonephritis
GNR gram-negative rods
GnRH gonadotropin-releasing hormone
GPA granulomatosis w/ polyangiitis
GPC gram-positive cocci
GPI glycoprotein IIb/IIIa inhibitor
GRA glucocorticoid-remediable aldosteronism
GU gastric ulcer
GVHD graft-versus-host disease
h hour
h/o history of
H2RA H2-receptor antagonist
HA headache
HAV hepatitis A virus
Hb hemoglobin
HBIG hepatitis B immunoglobulin
HBV hepatitis B virus
HCC hepatocellular carcinoma
HCM hypertrophic cardiomyopathy
Hct hematocrit
HCV hepatitis C virus
HCW health care worker
HD hemodialysis
HDL high-density lipoprotein
HDV hepatitis D virus
HELLP hemolysis, abnl LFTs, low plts
HEV hepatitis E virus
HF heart failure
HGPRT hypoxanthine-guanine phosphoribosyl transferase
HHS hyperosmolar hyperglycemic state

HIT heparin-induced thrombocytopenia
HK hypokinesis
HL Hodgkin lymphoma
HOB head of bed
HoTN hypotension
hpf high-power field
HPT hyperparathyroidism
HR heart rate
HRT hormone replacement therapy
HS hereditary spherocytosis
HSCT hematopoietic stem cell txp
HSM hepatosplenomegaly
HSP Henoch-Schönlein purpura
HSV herpes simplex virus
HTN hypertension
HUS hemolytic uremic syndrome
hx history
I&D incision & drainage
IABP intra-aortic balloon pump
IBD inflammatory bowel disease
IBS irritable bowel syndrome
IC inspiratory capacity
ICa ionized calcium
ICD implantable cardiac defibrillator
ICH intracranial hemorrhage
ICI immune checkpoint inhibitor
ICP intracranial pressure
ICU intensive care unit
IE infective endocarditis
IGF insulin-like growth factor
II integrase inhibitor
IIP idiopathic interstitial PNA
ILD interstitial lung disease
IMI inferior myocardial infarction
infxn infection
inh inhaled
INH isoniazid
INR international normalized ratio
IPAA ileal pouch-anal anastomosis

IPF idiopathic pulmonary fibrosis
ITP immune thrombocytopenia
IVB intravenous bolus
IVC inferior vena cava
IVDU intravenous drug use(r)
IVF intravenous fluids
IVIG intravenous immunoglobulin
JVD jugular venous distention
JVP jugular venous pulse
KS Kaposi's sarcoma
KUB kidney-ureter-bladder
LA left atrium long-acting lupus anticoagulant
LABA long-acting β_2-agonist
LAD left ant. descending cor. art. left axis deviation
LAE left atrial enlargement
LAN lymphadenopathy
LAP left atrial pressure leukocyte alkaline phosphatase
LBBB left bundle branch block
LCA left coronary artery
LCIS lobular carcinoma in situ
LCx left circumflex cor. art.
LDH lactate dehydrogenase
LDL low-density lipoprotein
LE lower extremity
LES lower esophageal sphincter
LFTs liver function tests
LGIB lower gastrointestinal bleed
LGV lymphogranuloma venereum
LH luteinizing hormone
LLQ left lower quadrant
LM left main coronary artery
LMWH low-molecular-weight heparin
LN lymph node
LOC loss of consciousness
LOS length of stay
LP lumbar puncture
lpf low-power field
LQTS long QT syndrome
LR lactated Ringer's

LUSB left upper sternal border
LV left ventricle
LVAD LV assist device
LVEDP LV end-diastolic pressure
LVEDV LV end-diastolic volume
LVESD LV end-systolic diameter
LVH left ventricular hypertrophy
LVOT left ventricular outflow tract
LVSD LV systolic dimension
mAb monoclonal antibody
MAC mitral annular calcification *Mycobacterium avium* complex
MAFLD metab. dysfxn-assoc. fatty liver dis.
MAHA microangiopathic hemolytic anemia
MALT mucosa-assoc. lymphoid tissue
MAO monoamine oxidase
MAP mean arterial pressure
MASH metab. dysfxn-assoc. steatohepatitis
MAT multifocal atrial tachycardia
MCD minimal change disease
MCP metacarpal phalangeal (joint)
MCS mechanical circulatory support
MCTD mixed connective tissue dis.
MCV mean corpuscular volume
MDI metered dose inhaler
MDMA 3,4-methylenedioxymethamphetamine (Ecstasy)
MDR multidrug resistant
MDS myelodysplastic syndrome
MEN multiple endocrine neoplasia
MG myasthenia gravis
MGUS monoclonal gammopathy of uncertain significance
MI myocardial infarction
min minute
min. minimal
MM multiple myeloma
MMEFR max. mid-expir. flow rate
MMF mycophenolate mofetil
MN membranous nephropathy
MNZ metronidazole
mo month

mod. moderate
MODS multiple organ dysfxn synd.
MPA microscopic polyangiitis
MPGN membranoproliferative glomerulonephritis
MPN myeloproliferative neoplasm
MR magnetic resonance mitral regurgitation
MRA magnetic resonance angiography mineralocorticoid receptor antagonist
MRCP MR cholangiopancreatography
MRI magnetic resonance imaging
MRSA methicillin-resistant *S. aureus*
MS mitral stenosis
MSA multisystem atrophy
MSK musculoskeletal
MTb *Mycobacterium tuberculosis*
mTOR mammalian target of rapamycin
MTP metatarsal phalangeal (joint)
MTX methotrexate
MV mitral valve
MVA mitral valve area
MVP mitral valve prolapse
MVR mitral valve replacement
Mφ macrophage
N/V nausea and/or vomiting
NAC *N*-acetylcysteine
NG nasogastric
NGT nasogastric tube
NHL non-Hodgkin lymphoma
niCMP non-ischemic CMP
NIF negative inspiratory force
NIV noninvasive ventilation
NJ nasojejunal
nl normal
NM neuromuscular
NMJ neuromuscular junction
NNRTI non-nucleoside reverse transcriptase inhibitor
NNT number needed to treat
NO nitric oxide
NPJT nonparoxysmal jxnal tachy.
NPO nothing by mouth

NPV negative predictive value
NRTI nucleoside reverse transcriptase inhibitor
NS normal saline
NSAID nonsteroidal anti-inflam. drug
NSCLC non-small cell lung cancer
NSF nephrogenic systemic fibrosis
NTG nitroglycerin
NVE native valve endocarditis
NYHA New York Heart Association
O&P ova & parasites
O/D overdose
o/w otherwise
OA osteoarthritis
OCP oral contraceptive pill
OG osmolal gap
OGT orogastric tube
OGTT oral glucose tolerance test
OI opportunistic infection
OM obtuse marginal cor. art.
OS overall survival
OSA obstructive sleep apnea
OTC over-the-counter
p/w present(s) with
PA pulmonary artery
PAC pulmonary artery catheter
PAD peripheral artery disease
PAN polyarteritis nodosa
PASP PA systolic pressure
PAV percutaneous aortic valvuloplasty
pb problem
PBC primary biliary cholangitis
PCI percutaneous coronary intervention
PCN penicillin
PCP *Pneumocystis jirovecii* pneumonia
PCR polymerase chain reaction
PCT porphyria cutanea tarda
PCWP pulm. capillary wedge pressure
PD Parkinson's disease peritoneal dialysis
PDA patent ductus arteriosus posterior descending cor. art.

PE pulmonary embolism
PEA pulseless electrical activity
PEEP positive end-expiratory pressure
PEF peak expiratory flow
PET positron emission tomography
PEx physical examination
PFO patent foramen ovale
PFS progression-free survival
PFT pulmonary function test
PGA polyglandular autoimmune synd.
PHT pulmonary hypertension
PI protease inhibitor
PID pelvic inflammatory disease
PIF prolactin inhibitory factor
PIP peak inspiratory pressure proximal interphalangeal (joint)
PKD polycystic kidney disease
PM polymyositis
PMF primary myelofibrosis
PMHx past medical history
PMI point of maximal impulse
PML progressive multifocal leukoencephalopathy
PMN polymorphonuclear leukocyte
PMR polymyalgia rheumatica
PMV perc. mitral valvuloplasty
PMVT polymorphic VT
PNA pneumonia
PND paroxysmal nocturnal dyspnea
PNH paroxysmal nocturnal hemoglobinuria
PNS peripheral nervous system
PO oral intake
POTS postural orthostatic tachycardia syndrome
PPH primary pulmonary HTN
PPI proton pump inhibitor
Pplat plateau pressure
PPM permanent pacemaker
PPV positive predictive value
Ppx prophylaxis
PR PR segment on ECG pulmonary regurgitation
PRBCs packed red blood cells

PRL prolactin

PRPP phosphoribosyl-1-pyrophosphate

PRWP poor R wave progression

PS pressure support pulmonic stenosis

PsA *Pseudomonas aeruginosa*

PSA prostate-specific antigen

PSC primary sclerosing cholangitis

PSGN poststreptococcal GN

PSHx past surgical history

PSV pressure support ventilation

Pt patient

PT prothrombin time

PTH parathyroid hormone

PTH-rP PTH-related peptide

PTT partial thromboplastin time

PTU propylthiouracil

PTX pneumothorax

PUD peptic ulcer disease

PUVA psoralen + ultraviolet A

PV polycythemia vera portal vein

PVD peripheral vascular disease

PVE prosthetic valve endocarditis

PVR pulmonary vascular resistance

PZA pyrazinamide

qac before every meal

qhs every bedtime

QoL quality of life

Qw Q wave

r/i rule in

r/o rule out

RA refractory anemia rheumatoid arthritis right atrium

RAA renin-angiotensin-aldosterone

RAD right axis deviation

RAE right atrial enlargement

RAI radioactive iodine

RAIU radioactive iodine uptake

RAS renal artery stenosis

RASi renin-angiotensin system inhibitor

RAST radioallergosorbent test
RBBB right bundle branch block
RBC red blood cell
RBF renal blood flow
RBV ribavirin
RCA right coronary artery
RCM restrictive cardiomyopathy
RCT randomized controlled trial
RDW red cell distribution width
RE reticuloendothelial
RF rheumatoid factor risk factor
RFA radiofrequency ablation
RHD rheumatic heart disease
RI reticulocyte index
RIBA recombinant immunoblot assay
RMSF Rocky Mountain spotted fever
ROS review of systems
RPGN rapidly progressive GN
RR respiratory rate
RRT renal replacement therapy
RT radiation therapy
RTA renal tubular acidosis
RTX rituximab
RUQ right upper quadrant
RUSB right upper sternal border
RV residual volume right ventricle
RVAD RV assist device
RVH right ventricular hypertrophy
RVOT RV outflow tract
RVSP RV systolic pressure
Rx therapy
RYGB Roux-en-Y gastric bypass
s/e side effect
s/p status post
s/s signs and symptoms
SA sinoatrial
SAAG serum-ascites albumin gradient
SAH subarachnoid hemorrhage
SB small bowel

SBE subacute bacterial endocarditis
SBO small bowel obstruction
SBP spontaneous bacterial peritonitis systolic blood pressure
SBT spontaneous breathing trial
SC subcutaneous
SCD sudden cardiac death
SCID severe combined immunodefic.
SCLC small cell lung cancer
Se sensitivity
sec second
SERM selective estrogen receptor modulator
sev. severe
SHBG steroid hormone binding globulin
SIADH synd. of inappropriate ADH
SIBO small intestine bacterial overgrowth
SIEP serum immunoelectrophoresis
SIHD stable ischemic heart disease
SIRS systemic inflammatory response syndrome
SJS Stevens-Johnson syndrome
SLE systemic lupus erythematosus
SMA superior mesenteric artery
SMV superior mesenteric vein
SMX sulfamethoxazole
SOS sinusoidal obstructive synd.
Sp specificity
SPEP serum protein electrophoresis
SR sinus rhythm
SSCY *Salmonella, Shigella, Campylobacter, Yersinia*
SSRI selective serotonin reuptake inhibitor
SSS sick sinus syndrome
SSZ sulfasalazine
ST sinus tachycardia
STD ST-segment depression
STE ST-segment elevation
STI sexually transmitted infection
SV stroke volume
SVC superior vena cava
SVR systemic vascular resistance
SVT supraventricular tachycardia

sx symptom(s) or symptomatic
T1D type 1 diabetes mellitus
T2D type 2 diabetes mellitus
TAA thoracic aortic aneurysm
TAVI transcatheter aortic valve implantation
TB tuberculosis
TBG thyroid-binding globulin
TCA tricyclic antidepressant
TCD transcranial Doppler
TCN tetracycline
Tdap tetanus, diphtheria, pertussis
TdP torsades de pointes
TdT terminal deoxynucleotidyl transferase
TEE transesophageal echo
TEER transcatheter edge-to-edge repair
tfn transfusion
TFTs thyroid function tests
TG triglycerides
TGA transposition of the great arteries
TIA transient ischemic attack
TIBC total iron binding capacity
TINU tubulointerstitial nephritis and uveitis
TIPS transjugular intrahepatic portosystemic shunt
TKI tyrosine kinase inhibitor
TLC total lung capacity
TLS tumor lysis syndrome
TMP trimethoprim
Tn troponin
TP total protein
TPMT thiopurine methyltransferase
TPN total parenteral nutrition
Tpo thrombopoietin
TPO thyroid peroxidase
TR tricuspid regurgitation
TRH thyrotropin-releasing hormone
TRS TIMI risk score
TRUS transrectal ultrasound
TS tricuspid stenosis
TSH thyroid-stimulating hormone

TSI thyroid-stimulating immunoglobulin
TSS toxic shock syndrome transsphenoidal surgery
TTE transthoracic echo
TTKG transtubular potassium gradient
TTP thrombotic thrombocytopenic purpura
TV tricuspid valve
Tw T wave
TWF T-wave flattening
TWI T-wave inversion
txp transplant
TZD thiazolidinediones
U/A urinalysis
U/S ultrasound
UA unstable angina
UAG urine anion gap
UC ulcerative colitis
UCx urine culture
UES upper esophageal sphincter
UFH unfractionated heparin
UGIB upper gastrointestinal bleed
UIP usual interstitial pneumonitis
ULN upper limit of normal
UOP urine output
UPEP urine protein electrophoresis
UR urgent revascularization
UrA uric acid
URI upper resp. tract infxn
UTI urinary tract infection
V/Q ventilation-perfusion
VAD ventricular assist device
VAP ventilator-associated PNA
VATS video-assisted thoracoscopic surgery
VBI vertebrobasilar insufficiency
VC vital capacity
VD vessel disease
VDRL Venereal Disease Research Laboratory (test for syphilis)
VEGF vascular endothelial growth factor
VEXAS vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic
VF ventricular fibrillation

VLDL very-low-density lipoproteins
VOD veno-occlusive disease
VS vital signs
VSD ventricular septal defect
V_T tidal volume
VT ventricular tachycardia
VTE venous thromboembolism
vWD von Willebrand's disease
vWF von Willebrand's factor
VZV varicella zoster virus
w/ with
w/o without
w/u workup
WBC white blood cell (count)
WCT wide-complex tachycardia
WHO World Health Organization
wk week
WM Waldenström's macroglobulinemia
WMA wall motion abnormality
WPW Wolff-Parkinson-White syndrome
XRT radiation therapy

INDEX

A

B

C

D

E

F

G

H

I

J

K

L

M

N

O

P

Q

R

S

T

U

V

W

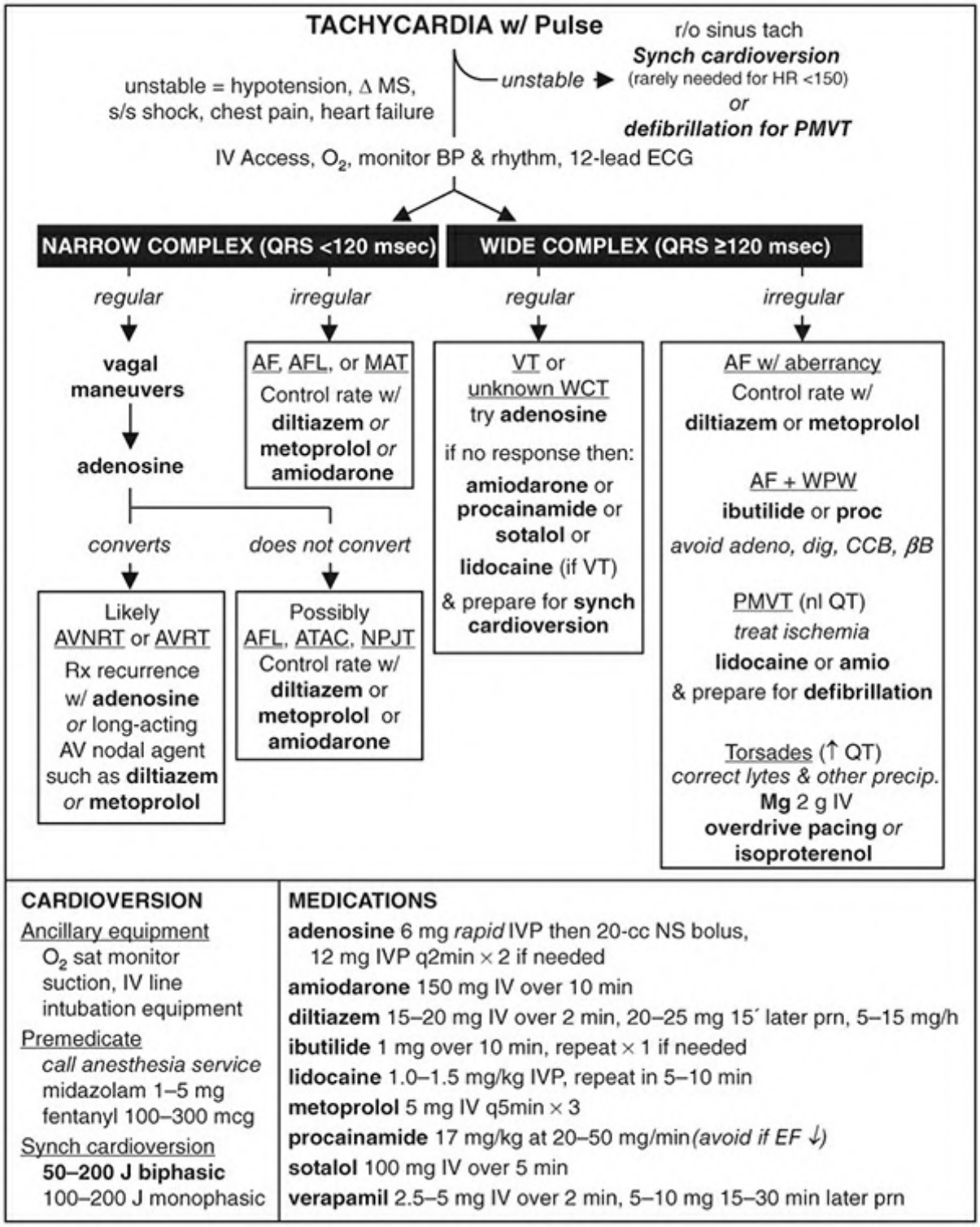
X

Y

Z

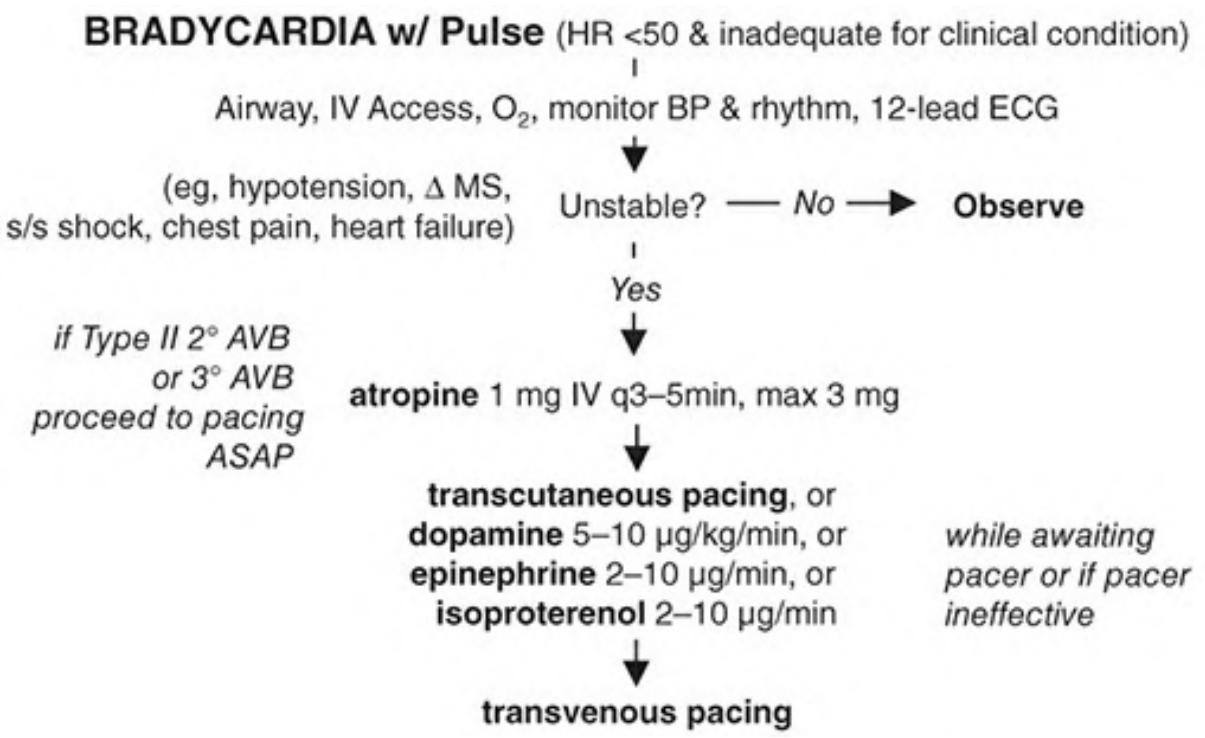
ACLS ALGORITHMS

Figure ACLS-1 ACLS Tachycardia Algorithm



(Adapted from ACLS 2020 Guidelines, *Circ* 2020;142(Suppl 2):S366)

Figure ACLS-2 ACLS Bradycardia Algorithm



(Adapted from ACLS 2020 Guidelines, *Circ* 2020;142(Suppl 2):S366)

Figure ACLS-3 VF/Pulseless VT, Asystole, & PEA Algorithms

PULSELESS ARREST

1. CPR

- **C**ompressions
  - **Push hard (2–2.4 inches) & fast (100–120/min)**
  - Minimize interruptions; rotate compressor q2min
- **A**irway: open airway (eg, head tilt-chin lift)
- **B**reathing: 10 breaths/min; 2 breaths q 30 compressions
  - Bag–mask acceptable; supplemental O_2

Attach monitor/defibrillator ASAP

2. ✓Rhythm (re✓q2min)

- **VT/VF → shock** (120–200 J biphas; 360 J mono)
- PEA → ✓ pulse
- Asystole → confirm in ≥1 lead (r/o fine VF)

3. Drug Therapy

4. Advanced Airway

5. Treat Rev Causes

Continuous CPR x 2 min

3. Drug Therapy

- Establish IV/IO access *(do not interrupt CPR)*
- **Epinephrine 1 mg IV q3–5min** (or 2 mg via ETT)
- **Amiodarone 300 mg IVB;** 2nd dose 150 mg
- **Lidocaine 1–1.5 mg/kg IVB (~100 mg);** 2nd dose 0.5–0.75 mg/kg
- Magnesium 1–2 g IV only for TdP

4. Consider Advanced Airway

- Endotracheal intubation or supraglottic advanced airway
- Clinical assessment: bilat. chest expansion & breath sounds
- Device to ✓ tube placement
  - Continuous waveform capnography (~100% Se & Sp)
  - Colorimetric exhaled CO_2 detection (≈clinical assess.); false neg w/ ineffective CPR, PE, pulm. edema, etc.
- 10 breaths per min w/ continuous compressions

5. Treat Reversible Causes

- Hypovolemia: volume
- Hypoxia: oxygenate
- H^+ ions (acidosis): $NaHCO_3$
- Hypo/hyper K: KCl/Ca et al.
- Hypothermia: warm
- Tension PTX: needle decomp.
- Tamponade: pericardiocent.
- Toxins: med-specific
- Thromb. (PE): lysis, thrombect.
- Thromb. (ACS): PCI or lysis